PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No.: 4,639,436 Issued: 27 January 1987 #40

Patentee: Junge et al. Title: Antidiabetic 3,4,5-Trihydroxypiperidines

Assignee: Bayer Aktiengesellschaft

Date: 12 February 1997

Box Patent Extension
Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

SUPPLEMENT TO APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC 156 et seq. AND 37 CFR 1.710 et seq.

Transmitted herewith as requested by the Examiner is a corrected Declaration amended to included the language required by 37 CFR 1.740(b)(2) which was inadvertently omitted in the original declaration.

The original Declaration will be hand-carried to the PTO on 13 February 1997, together with a certified copy.

The Commissioner is hereby authorized to charge any fees required as a result of this submission to Deposit Account No. 13-3372. A duplicate of this sheet will be enclosed with the original.

Respectfully submitted,

Barbara A. Shimei

Barbara A. Shimei, Esq.
Registration No. 29,862
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516

Phone: (203) 812-2786
Fax: (203) 812-5492

(17) **DECLARATION OF ATTORNEY:**

I hereby declare that all statements made herein of my own knowledge are true; that all statements made on information and belief are believed to be true; that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application; that I am a patent attorney authorized to practice before the United States Patent and Trademark Office; that Bayer Corporation has been granted certain rights under the subject patent by its parent company Bayer AG; that Bayer Corporation's predecessor in interest Miles Inc. was the sponsor of the subject IND and Bayer Corporation was the sponsor of the subject NDA; that Miles Inc. and Bayer Corporation was/is an affiliate of Bayer AG and sublicensed by Bayer AG to market approved products in the United States; that by virtue of the enclosed Power of Attorney duly signed by Bayer AG I am an authorized designee of Bayer AG for the purpose of submitting this application for patent term extension, and hence, have the authority to submit and prosecute this application on behalf of Bayer AG; that I have reviewed and understand the contents of the application that is being submitted herewith; that I believe the subject patent is subject to extension pursuant to 37 CFR 1.710; that I believe an extension of the length claimed is justified under 35 USC 156 and the applicable regulations; and that I believe that the subject patent meets the conditions for term extension as set forth in 37 CFR 1.720.

Respectfully submitted,

Barbara A. Shimei

Barbara A. Shimei, Esq.
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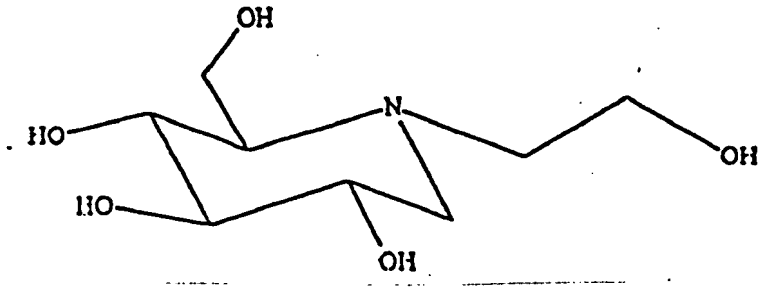
Cheryl

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 37 CFR 1.710

(1) **A COMPLETE IDENTIFICATION OF THE APPROVED PRODUCT:**

GLYSET tablets contain miglitol, an oral alpha-glucosidase inhibitor for use in the management of non-insulin-dependent diabetes mellitus (NIDDM). Miglitol is a desoxynojirimycin derivative, and is chemically known as 3,4,5-piperidinetriol, 1-(2-hydroxyethyl)-2-(hydroxymethyl)-,[2R-(2α,3β,4α,5β)]-. It is a white to pale-yellow powder with a molecular weight of 207.2. Miglitol is soluble in water and has a pK_a of 5.9. Its empirical formula is $C_8H_{17}NO_5$ and its chemical structure is as follows:



GLYSET tablets are available as 25 mg, 50 mg, and 100 mg tablets for oral use. The inactive ingredients are starch, microcrystalline cellulose, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, polysorbate 80, and iron oxide. For further details see attached Exhibits A1 and A2.

(2) **A COMPLETE IDENTIFICATION OF THE FEDERAL STATUTE UNDER WHICH THE REGULATORY REVIEW OCCURRED:**

The regulatory review occurred under Section 505(b) of the Federal Food, Drug, and Cosmetic Act, 21 USC 355(b) et seq. ("FFDCA").

(3) **AN IDENTIFICATION OF THE DATE ON WHICH THE PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR USE:**

Miglitol was approved by the FDA for commercial marketing pursuant to Section 505(b) of the FFDCA on 18 December 1996.

(4) **AN IDENTIFICATION OF EACH ACTIVE INGREDIENT IN THE PRODUCT AND AS TO EACH ACTIVE INGREDIENT, A STATEMENT THAT IT HAS NOT BEEN PREVIOUSLY APPROVED FOR COMMERCIAL MARKETING OR USE UNDER THE FFDCA:**

The sole active ingredient of the approved new drug (which is a human drug) is miglitol as identified above under Section 1. Miglitol has not been previously approved for commercial marketing or use under the FFDCA.

(5) **A STATEMENT THAT THE APPLICATION IS BEING SUBMITTED WITHIN THE SIXTY DAY PERIOD PERMITTED FOR SUBMISSION PURSUANT TO SECTION 1.720(f) AND AN IDENTIFICATION OF THE DATE OF THE LAST DAY ON WHICH THE APPLICATION COULD BE SUBMITTED:**

This application is expected to be hand-delivered to the United States Patent and Trademark Office on 11 February 1997 which is within the sixty day period starting on 18 December 1996 and ending on 16 February 1997.

(6) **A COMPLETE IDENTIFICATION OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT:**

A complete identification of the patent is presented as follows:

Names of the Inventors: Bodo Junge, Hans P. Krause, Lutz Müller, and Walter Puls
Patent Number: 4,639,436
Date of assignment: 14 August 1978 (copy attached as Exhibit C)
Issue Date: 27 January 1987
Date which is 17 years from the date of issue: 27 January 2004
Date which is 20 years from the earliest U.S. priority date: 23 August 1998

(7) **A COPY OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT:**

A copy of said patent is attached hereto as Exhibit B.

(8) **A COPY OF ANY DISCLAIMER, CERTIFICATE OF CORRECTION, RECEIPT OF MAINTENANCE FEE PAYMENT, OR REEXAMINATION CERTIFICATE ISSUED IN THE PATENT:**

A Certificate of Correction was issued on 19 May 1987; a copy is attached hereto as Exhibit D.

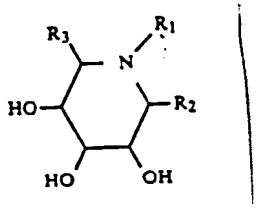
This patent is not subject to maintenance fees.

No statutory disclaimer under 35 USC 253(a) or re-examination certificate has been applied for or issued for this patent.

(9) **A STATEMENT THAT THE PATENT CLAIMS THE APPROVED PRODUCT OR A METHOD OF USING THE APPROVED PRODUCT, AND A SHOWING WHICH LISTS EACH APPLICABLE PATENT CLAIM AND DEMONSTRATES THE MANNER IN WHICH EACH APPLICABLE PATENT CLAIM READS ON THE APPROVED PRODUCT OR A METHOD OF USING THE APPROVED PRODUCT:**

USP 4,639,436 claims miglitol, pharmaceutical compositions and medicaments containing miglitol, and methods of combating diabetes using miglitol.

Claim 1 covers compounds of the formula



in which R_1 is . . . substituted C_1-C_4 alkyl. . . said substituted C_1-C_4 alkyl being substituted by hydroxy . . . R_2 is -H . . . R_3 is . . .-CH_2OH . . . . Miglitol is the compound wherein R_1 is -CH_2CH_2OH; R_2 is -H; and R_3 is -CH_2OH.

Claim 5 covers the compounds according to claim 1 wherein R_2 is -H, -SO_3H or -CN. Miglitol is the compound according to claim 1 wherein R_1 is -CH_2CH_2OH; R_2 is -H, and R_3 is -CH_2OH.

Claim 6 covers the compounds according to claim 5 wherein R_2 is -H. Miglitol is the compound according to claim 5 wherein R_1 is -CH_2CH_2OH; R_2 is -H, and R_3 is -CH_2OH.

Claim 7 covers the compounds according to claim 1 in which R_3 is -H, -CH_2OH, -CH_3, -CH_2NH_2, -CH_2NH or -CH_2-O-(C_1-C_6-alkyl). Miglitol is the compound according to claim 1 in which R_1 is -CH_2CH_2OH; R_2 is -H, and R_3 is -CH_2OH.

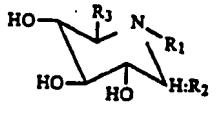
Claim 8 covers the compounds according to claim 1 in which R_3 is -CH_2OH. Miglitol is the compound according to claim 1 in which R_1 is -CH_2CH_2OH; R_2 is -H, and R_3 is -CH_2OH.

Claim 9 covers the compounds according to claim 1 in which R_2 is -H and R_3 is -CH_2OH. Miglitol is the compound according to claim 1 in which R_1 is -CH_2CH_2OH; R_2 is -H, and R_3 is -CH_2OH.

Claim 10 covers the compounds of claim 1 in which R_1 is C_1-C_4 alkyl substituted by hydroxy or mercapto. Miglitol is the compound according to claim 1 in which R_1 is -CH_2CH_2OH; R_2 is -H, and R_3 is -CH_2OH.

Claim 14 is the compound of claim 1 which is N-(β-hydroxyethyl)-1-desoxynojirimycin. This is an alternate name for miglitol.

Claim 17 covers compounds of claim 1 with the steric formula



Miglitol has this steric formula.

Claim 18 covers a pharmaceutical composition for the treatment of diabetes, hyperlipaemia or adiposity containing as an active ingredient an effective amount for the treatment of diabetes, hyperlipaemia or adiposity of a compound according to claim 1 in admixture with a solid or liquefied gaseous diluent or in admixture with a liquid diluent other than a solvent of a molecular weight less than 200 except in the presence of a surface-active agent. The approved product is a pharmaceutical composition for the treatment of diabetes containing as an active ingredient an effective amount for the treatment of diabetes of miglitol in admixture with a solid diluent.

Claim 20 covers a composition according to claim 18 or 19 containing from 0.5 to 95% by weight of the said active ingredient. The approved product is a composition according to claim 18 in the form of tablets containing 25, 50, or 100 mg miglitol. The 25-mg tablet contains 39.1% miglitol by weight; the 50-mg tablet contains 39.4% miglitol by weight, and the 100-mg tablet contains 39.4% miglitol by weight.

Claim 21 covers a medicament in dosage unit form for the treatment of diabetes, hyperlipaemia or adiposity comprising an effective amount for the treatment of diabetes, hyperlipaemia or adiposity of a compound according to claim 1 and an inert pharmaceutical carrier. The approved product is a medicament in dosage unit form for the treatment of diabetes, comprising an amount of miglitol effective for the treatment of diabetes and an inert pharmaceutical carrier.

Claim 22 covers a medicament of claim 21 in the form of tablets, pills, dragees, capsules, ampoules, or suppositories. The approved product is a medicament according to claim 21 available in the form of tablets containing 25, 50, or 100 mg miglitol.

Claim 23 covers a pharmaceutical composition for the treatment of diabetes, hyperlipaemia or adiposity containing as an active ingredient an effective amount for the treatment of diabetes, hyperlipaemia, or adiposity of a compound according to claim 17 in admixture with a solid or liquefied gaseous diluent or in admixture with a liquid diluent other than a solvent of a molecular weight less than 200 except in the presence of a surface-active agent. The approved product is a pharmaceutical composition for the treatment of diabetes containing as an active ingredient an effective amount for the treatment of diabetes of miglitol, in the configuration shown in claim 17, in admixture with a solid diluent.

Claim 25 covers a medicament in dosage unit form comprising an effective amount for the treatment of diabetes, hyperlipaemia or adiposity of a compound according to claim 17 and an inert pharmaceutical carrier. The approved product is a medicament in dosage unit form comprising an effective amount for the treatment of diabetes of miglitol according to claim 17 and an inert pharmaceutical carrier.

Claim 26 covers a medicament of claim 25 in the form of tablets, pills, dragees, capsules, ampoules, or suppositories. The approved product is a medicament according to claim 25 available in the form of tablets containing 25, 50, or 100 mg miglitol.

Claim 27 covers a method of combating adiposity, diabetes and/or hyperlipaemia in warm-blooded animals which comprises administering to the said animal an effective amount for the treatment of diabetes, hyperlipaemia or adiposity of an active compound according to claim 1 either alone or in admixture with a diluent or in the form of a medicament. The claimed method applies to combating diabetes in humans by administering an effective amount for the treatment of diabetes of miglitol in admixture with a diluent or in the form of a medicament.

Claim 28 covers a method according to claim 27 in which the active compound is administered in an amount of 0.01 mg to 100 mg per kg body weight per day. The approved miglitol product is administered in dosages of from 75-300 mg/day, which is equivalent to 1.5-6 mg/kg body weight per day for an average (50 kg) female and 1.07-4.29 mg/kg body weight per day for an average (70 kg) male.

Claim 30 covers a method according to claim 27 in which the active compound is administered orally. The approved miglitol product is administered orally.

Claim 31 covers a method of combating adiposity, diabetes and/or hyperlipaemia in warm-blooded animals which comprises administering to the animals an effective amount for the treatment of diabetes, hyperlipaemia or adiposity of an active compound according to claim 17 either alone or in admixture with a diluent or in the form of a medicament. The claimed method applies to combating diabetes in humans by administering an effective amount for the treatment of diabetes of miglitol in the configuration given in claim 17 in admixture with a diluent or in the form of a medicament.

(10) **A STATEMENT OF THE RELEVANT DATES AND INFORMATION PURSUANT TO 35 USC 156(g) IN ORDER TO ENABLE THE SECRETARY OF HEALTH AND HUMAN SERVICES TO DETERMINE THE APPLICABLE REGULATORY REVIEW PERIOD:**

Date on which IND 22,316 was submitted: 17 June 1983

Date on which IND 22,316 was received by the FDA: 22 June 1983

Effective date of IND: 22 July 1983

Date on which NDA 20-682 was submitted: 28 December 1995

Date on which NDA 20-682 was received by the FDA: 29 December 1995

Date on which NDA 20-682 was approved: 18 December 1996

(11) **A BRIEF DESCRIPTION OF THE SIGNIFICANT ACTIVITIES UNDERTAKEN BY THE MARKETING APPLICANT DURING THE APPLICABLE REGULATORY REVIEW PERIOD WITH RESPECT TO THE APPROVED PRODUCT AND THE SIGNIFICANT DATES APPLICABLE TO SUCH ACTIVITIES:**

By virtue of a license agreement between the record owner of the subject patent and Miles Inc. (a wholly-owned subsidiary of Bayer AG), the latter obtained certain rights under the subject patent including the right to market the approved drug in the United States.

Miles Inc. submitted IND 22,316 for miglitol tablets on 17 June 1983. This IND was received by the FDA on 22 June 1983 and became effective on 22 July 1983.

Bayer Corporation submitted NDA 20-682 on 28 December 1995. This NDA was received by the FDA on 29 December 1995 and approved on 18 December 1996 for miglitol as a monotherapy adjunct to diet to improve glycemic control in patients with non-insulin-dependent diabetes mellitus (NIDDM) whose hyperglycemia cannot be managed with diet alone. Miglitol may also be used in combination with sulfonyl urea when diet plus either miglitol or sulfonylurea alone do not result in adequate glycemic control.

On April 1, 1995 Miles Inc. changed its name to Bayer Corporation. Bayer Corporation believes that it and its predecessor Miles Inc. pursued their activities with due diligence throughout the regulatory review period, namely, the testing phase and the approval phase. Significant activities undertaken by Miles Inc./Bayer Corporation during the regulatory review period are briefly described in Exhibits E1 and E2. The former relates to the testing phase, whereas the latter relates to the approval phase.

(12) **A STATEMENT THAT IN THE OPINION OF THE APPLICANT THE PATENT IS ELIGIBLE FOR THE EXTENSION AND A STATEMENT AS TO THE LENGTH OF EXTENSION CLAIMED, INCLUDING HOW THE LENGTH OF EXTENSION WAS DETERMINED:**

Applicant believes that the subject patent is eligible for patent term extension pursuant to 35 USC 156(a) and 37 CFR 1.710 for the following reasons:

(1) The patent claims the approved drug product or method (see Section 9);

(2) The term of this patent has never been extended and there are no other extensions under 35 USC 156(c)(4);

(3) This application for patent term extension is submitted by an authorized agent of the record owner of the subject patent;

(4) The product has been subject to a regulatory review period before its commercial marketing or use as evident from Section 11 above; and

(5) The permission for the commercial marketing or use of the product after said regulatory review period is the first commercial marketing or use of the product under the provisions of the FFDCA.

Applicant believes that the subject patent is entitled to 1827 days of term extension. This length of extension has been calculated as follows. Details of the key days are presented as Exhibit F.

(1) Number of days of the testing phase is 4543 days (between 22 July 1983 and 29 December 1995);

(2) Number of days of the approval phase is 355 days (between 29 December 1995 and 18 December 1996). The sponsor of the subject IND and NDAs acted in due diligence during the relevant periods as evident from the aforementioned Exhibits E1 and E2;

(3) One half of the testing period is 2271 days;

(4) The sum of the period recited under Paragraph 12(3) and the period recited under Paragraph 12(2) of this section is 2626 days (modified regulatory review period);

(5) The subject patent issued subsequent to 24 September 1984 (effective date of the 1984 Waxman-Hatch Act);

(6) The date of approval of the subject NDA is 18 December 1996;

(7) The date which is 17 years from the issue date is 27 January 2004;

(8) The date which is 20 years from the earliest US priority date is 23 August 1998;

(9) Addition of the modified regulatory review period of 2626 days recited under Paragraph 12(4) above would extend the expiration date of the subject patent to 6 April 2011;

(10) The extension period is subject to the five-year limitation under 35 USC 156(g)(6)(A) and hence, the subject patent cannot be extended beyond 27 January 2009;

(11) The patent term extension is also subject, under 35 USC 156(c)(3) to the fourteen year limitation as to the net effective life of the patent after the NDA approval. This limitation dictates that the subject patent cannot be extended beyond 18 December 2010.

(12) In light of the conclusions stated under Paragraphs 12(9), 12(10), and 12(11), the extended expiration date is greater than the five year limitation set forth in USC 156(g)(6)(A) and greater than the fourteen year limitation recited under Paragraph 12(11). Thus, the extended expiration date of the subject patent is believed to be 27 January 2009, namely 1827 days after the date of the 17-year term (extension from 27 January 2004 to 27 January 2009).

13. **APPLICANT'S ACKNOWLEDGMENT OF DUTY TO DISCLOSE:**

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services under 37 CFR 1.765 any information which is material to the determination of entitlement for the extension sought herein.

14. **THE PRESCRIBED FEE FOR RECEIVING AND ACTING UPON THE APPLICATION FOR EXTENSION:**

Please charge Deposit Account Number 13-3372 (Bayer Corporation) in the amount of $1,090.00 (One Thousand Thirty Dollars) as the fee covering the instant applicant for patent term extension. The Commissioner is hereby authorized to charge any additional fees which may be required or credit any overpayment to Account No. 13-3372. A duplicate copy of this sheet is enclosed.

15. **THE NAME, ADDRESS, AND TELEPHONE NUMBER OF THE PERSON TO WHOM INQUIRIES AND CORRESPONDENCE RELATING TO THE APPLICATION FOR PATENT TERM EXTENSION ARE TO BE DIRECTED:**

Please forward all inquiries and correspondence relating to this application for patent extension to:

Jeffrey M. Greenman, Esq.
Registration No. 26,552
Vice President, Patents and Licensing
Bayer Corporation
Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516
Telephone: (203) 812-2037
Fax: (203) 812-5492

(16) A DUPLICATE OF THE APPLICATION PAPERS, CERTIFIED AS SUCH:

A duplicate of this Application, certified as such, is enclosed herewith. Also enclosed are three (3) copies for the convenience of the Examiner.

(17) DECLARATION OF ATTORNEY:

I hereby declare that all statements made herein of my own knowledge are true; that all statements made on information and belief are believed to be true; that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application; that I am a patent attorney authorized to practice before the United States Patent and Trademark Office; that Bayer Corporation has been granted certain rights under the subject patent by its parent company Bayer AG; that Bayer Corporation's predecessor in interest Miles Inc. was the sponsor of the subject IND and Bayer Corporation was the sponsor of the subject NDA; that Miles Inc. and Bayer Corporation was/is an affiliate of Bayer AG and sublicensed by Bayer AG to market approved products in the United States; that by virtue of the enclosed Power of Attorney duly signed by Bayer AG I am an authorized designee of Bayer AG for the purpose of submitting this application for patent term extension, and hence, have the authority to submit and prosecute this application on behalf of Bayer Corporation; that I believe the subject patent is subject to extension pursuant to 37 CFR 1.710; that I believe an extension of the length claimed is justified under 35 USC

156 and the applicable regulations; and that I believe that the subject patent meets the conditions for term extension as set forth in 37 CFR 1.720.

Respectfully submitted,

Barbara A. Shimei

Barbara A. Shimei, Esq.
Reg. No. 29,862
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516

Telephone: (203) 812-2786
Fax: (203) 812-5492

Exhibit A A1: summary of chemical and physical properties of miglitol
A2: package insert

Exhibit B: copy of USP 4,639,436

Exhibit C: copy of assignment

Exhibit D: copy of Certificate of Correction

Exhibit E1: testing phase during IND 22,316

Exhibit E2: approval phase for NDA 20-682

Exhibit F: key dates in calculation

I hereby certify the attached is a true copy of the accompanying application for extension of the term of US Patent 4,639,436 under 35 USC 156 including its exhibits and supporting papers.

Barbara A. Shimei

Barbara A. Shimei, Esq.
Registration No. 29,862
Attorney for applicant
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516

Date: 10 February 1997

ORIGINAL

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No.:4,639,436 Issued: 27 January 1987

Patentee: Junge et al. Title: Antidiabetic 3,4,5-Trihydroxypiperidines

Assignee: Bayer Aktiengesellschaft

Date: 11 February 1997

Box Patent Extension
Commissioner of Patents andTrademarks
Washington, DC 20231

Sir:

LETTER OF TRANSMITTAL OF APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC 156 et seq. and 37 CFR 1.710 et seq.

Transmitted herewith for filing is an application for extension of term of the above-identified patent and a duplicate of said application papers, certified as such. Also enclosed are three (3) additional copies for the convenience of the Examiner.

The content of the application consists of:

14 pages of information and various statements made by Bayer AG (assignee of record of U.S. Patent 4,639,436) and the undersigned attorney pursuant to 35 USC 156 et seq. and 37 CFR 1.710 et seq.

6 pages of Exhibit A1

18 pages of Exhibit A2

36 pages of Exhibit B

1 page of Exhibit C

3 pages of Exhibit D

4 pages of Exhibit E1

4 pages of Exhibit E2

1 page of Exhibit F

Submitted concurrently herewith is a Power of Attorney duly signed by Bayer AG appointing the undersigned to file and prosecute this application for patent term restoration on its behalf.

The Commissioner is hereby authorized to charge payment of any fees associated with this communication or credit any overpayment to Deposit Account No. 13-3372. A duplicate of this sheet is enclosed.

Respectfully submitted,

Barbara A. Shimei

Barbara A. Shimei, Esq.
Reg. No. 29,862
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516

Telephone: (203) 812-2786
Fax: (203) 812-5492

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No.: 4,639,436 Issued: 27 January 1987

Patentee: Bayer Aktiengesellschaft Title: Antidiabetic 3,4,5-Trihydroxypiperidines

Box Patent Extension
Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

POWER OF ATTORNEY

Bayer Aktiengesellschaft, assignee of record of the entire interest of the above-identified patent, hereby grants to Jeffrey M. Greenman, Reg. No. 26,552, Barbara A. Shimei, Reg. No. 29,862, William F. Gray, Reg. No. 31,018, Alice A. Brewer, Reg. No. 32,888, and Huw R. Jones, Reg. No. 33,916, complete power of attorney to prosecute the application for extension of the term of the above-identified patent, to transact all business in the Patent and Trademark Office connected therewith, and to receive any certification of extension of patent term. Please send correspondence to:

Jeffrey M. Greenman, Esq.
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516
Telephone: (203) 812-2037
Fax: (203) 812-5492

Attached to this power is a Certificate Under 37 CFR 3.73(b).

Respectfully submitted,

BAYER AKTIENGESELLSCHAFT

By: _____ By: _____

Name: Dr. Schauerte Name: Dr. Ehrenstein

Title: Secretary Title: Secretary

Date: February 3, 1997 Date: February 3, 1997

Assignment to Bayer AG recorded at USPTO on 23 August 1978 at Reel 3576 Frame 769

CERTIFICATE UNDER 37 CFR 3.73(b)

Inventors: Bodo Junge, Hans P. Krause, Lutz Mueller and Walter Puls

Patent No.: 4,639,436 Date Issued: January 27, 1987

Application No: 936,280 Date Filed: August 23, 1978

Title: Antidiabetic 3,4,5-Trihydroxypiperidines

Bayer Aktiengesellschaft, a corporation, certifies that it is the assignee of the entire right, title and interest in the patent identified above by virtue of an assignment from the inventors as recorded in the United States Patent and Trademark Office at Reel 3576, Frame 769 on 23 August 1978.

The undersigned has reviewed all the documents in the chain of title of the patent identified above and, to the best of the undersigned's knowledge and belief, title is in the assignee identified above.

The undersigned (whose title is supplied below) is empowered to sign this certificate on behalf of the assignee.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature: _____ Signature: _____

Name: Dr. Schauerte Name: Dr. Ehrenstein

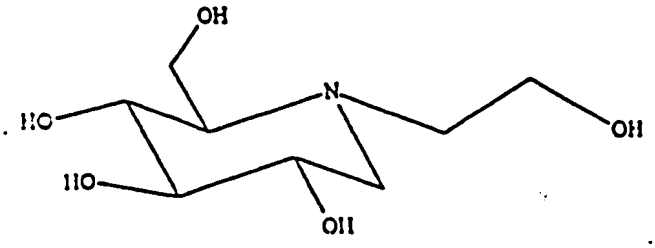
Title: Secretary Title: Secretary

Date: February 3, 1997 Date: February 3, 1997

Chemical and Physical Properties

1 Structure

1.1 Structural formula



1.2 Empirical formula
$C_8H_{17}NO_5$

1.3 Rel. molecular mass
207.2 g/mol

1.4 Chemical name
1,5-Dideoxy-1,5-[(2-hydroxyethyl)imino]-D-glucitol

According to Iupac: (2R, 3R, 4R, 5S)-1-(2-Hydroxyethyl)-2-(hydroxymethyl)-3,4,5-piperidinetriol

According to USAN: 3,4,5-Piperidinetriol-1,(2-hydroxyethyl)-2-(hydroxymethyl)-,[2R-(2α, 2β, 4α, 5β)]

2 Description
White to pale yellowish substance

3 Melting behaviour
The substance melts at 145-147°C (capillary method according to DAB).

4 Hygroscopicity
The substance is not hygroscopic. The weight increase after 14 day's storage at room temperature and relative humidities of 30, 60 and 90 % is 0.0 %.

5 Polymorphism

The active ingredient miglitol was tested for polymorphism by IR spectroscopy and thermal analysis (differential scanning calorimetryk, thermogravimetry and thermomicroscopy). The active ingredient crystallized in the same crystal form in all tests with a melting range of 145 - 147 °C. Even after 6 months storage at -40°C, +25°C and +50°C and after grinding and crystallization from solvents and the melt, the crystals do no transform into a different modification.

6 Spezific rotation

The specific rotation $[\alpha]_D^{20}$ is 7.8° (-).

Test apparatus:	Polarimeter 241, Perkin Elmer
Concentration:	1.2 g in 50 ml water
Active ingredient batch	513252 with assay, based on the dried substance 99,7%.

7 Spezific absorption

Miglitol exhibits maximum absorption at approx. 200 nm.

8 Solubility

Solvent	Temperature (°C)	Solubility (mg/100ml)
Water	37	79100
0.1 M HCl	37	79400
Phosphate buffer pH 6.8 DAB (10 %)	37	78800
Isopropanol	25	114
Acetonitrile	25	7.4
Ethyl acetate	25	1.4
Dichloromethane	25	< 1
n-Heptane	25	< 1

Test conditions

The substance (batch no. 509283 and 513252) was stirred with the test solvent in a thermostatically controlled water bath for 20 hours and passed through a 0.45 µm membrane filter or black band paper filter (the first three). The dissolved active ingredient was determined by HPLC (see attachment 1).

A comparative solubility determination in water at 37°C of substance prepared according to the ethylene oxide process and glyoxal process did not reveal any significant differences.

9 Ionisation constants (pK_a-value)

pK_a-value: 5.9

Test conditons: (potentiometric method)

Solution:	0.003 molar solution in 0.01 M hydrochloric acid
Titrant:	0.1M sodium hydroxide solution (back titration)
Electrode:	Combined glass/calomel
Apparatus:	Mettler Titrator DL 25
Measurement temperature:	25 °C
Batch no:	507300

10 Partition coefficient (P)

System	P	log P
Octanol/water	0.0022	-2.7
Octanol/0.1 M HCl	< 0.001	< -3
Octanol/0.1 M NaOH	0.0019	-2.7

Test conditions

In a conical flask, 20 ml each of the upper and lower phases were shaken meachanically at room temperature for 16 hours. The phases were separated and subsequently the active ingredient content was determined by high performance liquid chromatography (see attachment 1).
Batch no. 513252.

11 Stability Batch no.: 513252

Stability against	Test substance	Conditions	Assessment
Temperature	substance	3 months 70°C	stable
Temperature and moisture	substance	6 months 40°C and 75% rel. humidty	stable
Light (Test in white glass)	substance	24 h xenon light	stable
	0.1 % solution in water	24 h xenon light	stable
Hydrolysis	0.1 % solution in water	24 h at 90°C	stable
Hydrolysis	0.1 % solution in 0.1 M HCl	24 h at 90°C	stable
Hydrolysis	0.1 % solution in phosphate buffer pH 8.0 (1:10)	24 h at 90°C	stable
Hydrolysis	0.1 % solution in 0.1M NaOH	24 h at 90°C	stable
Oxidation	0.1 % solution in water with 0.3% hydrogen peroxide	24 h at 25°C	unstable: 40 % content decrease
	0,1 %i solution in water and oxygen aeration	32 h at 25°C	stable

Attachment 1

Analytical method (HPLC)

Column:	Asahipak NH2P ,5µm material, length: 25 cm, I.D. 4.6 mm
Volume injected:	15 and 20 µl
Eluent:	Acetonitrile / phosphate buffer (77 : 23 v/v)
Flow:	1.0 ml/min
Temperature of column oven:	35°C
Detection:	UV, 210 nm

NDA 20-682
Dec. 18, 1996

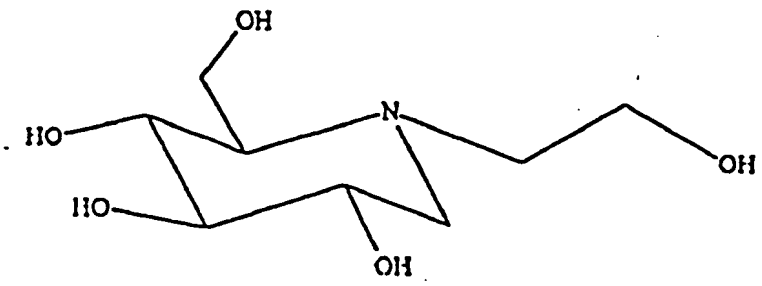
PROPOSED TEXT OF LABELING (PACKAGE INSERT)

GLYSET™

(miglitol) tablets

DESCRIPTION

GLYSET tablets contain miglitol, an oral alpha-glucosidase inhibitor for use in the management of non-insulin-dependent diabetes mellitus (NIDDM). Miglitol is a desoxynojirimycin derivative, and is chemically known as 3,4,5-piperidinetriol, 1-(2-hydroxyethyl)-2-(hydroxymethyl)-, [2R-(2α,3β,4α,5β)]-. It is a white to pale-yellow powder with a molecular weight of 207.2. Miglitol is soluble in water and has a pK_a of 5.9. Its empirical formula is $C_8H_{17}NO_5$ and its chemical structure is as follows:



GLYSET tablets are available as 25 mg, 50 mg and 100 mg tablets for oral use. The inactive ingredients are starch, microcrystalline cellulose, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, polysorbate 80, and iron oxide.

CLINICAL PHARMACOLOGY

Miglitol is a desoxynojirimycin derivative that delays the digestion of ingested carbohydrates, thereby resulting in a smaller rise in blood glucose concentration following meals. As a consequence of plasma glucose reduction, GLYSET reduces levels of glycosylated hemoglobin in patients with Type II (non-insulin-dependent) diabetes mellitus. Systemic nonenzymatic protein glycosylation, as reflected by levels of glycosylated hemoglobin, is a function of average blood glucose concentration over time.

Mechanism of Action: In contrast to sulfonylureas, GLYSET does not enhance insulin secretion. The antihyperglycemic action of miglitol results from a reversible inhibition of membrane-bound intestinal α-glucoside hydrolase enzymes. Membrane-bound intestinal α-glucosidases hydrolyze oligosaccharides and disaccharides to glucose and other monosaccharides in the brush border of the small intestine. In diabetic patients, this enzyme inhibition results in delayed glucose absorption and lowering of postprandial hyperglycemia.

Because its mechanism of action is different, the effect of GLYSET to enhance glycemic control is additive to that of sulfonylureas when used in combination. In addition, GLYSET diminishes the insulinotropic and weight-increasing effects of sulfonylureas.

Miglitol has minor inhibitory activity against lactase and consequently, at the recommended doses, would not be expected to induce lactose intolerance.

Pharmacokinetics:

Absorption: Absorption of miglitol is saturable at high doses: a dose of 25 mg is completely absorbed, whereas a dose of 100 mg is only 50% - 70% absorbed. For all doses, peak concentrations are reached in 2-3 hours. There is no evidence that systemic absorption of miglitol contributes to its therapeutic effect.

Distribution: The protein binding of miglitol is negligible (<4.0%). Miglitol has a volume of distribution of 0.18 L/kg, consistent with distribution primarily into the extracellular fluid.

Metabolism: Miglitol is not metabolized in man or in any animal species studied. No metabolites have been detected in plasma, urine, or feces, indicating a lack of either systemic or pre-systemic metabolism.

Excretion: Miglitol is eliminated by renal excretion as unchanged drug. Thus, following a 25-mg dose, over 95% of the dose is recovered in the urine within 24 hours. At higher doses, the cumulative recovery of drug from urine is somewhat lower due to the incomplete bioavailability. The elimination half-life of miglitol from plasma is approximately 2 hours.

Special Populations:

Renal Impairment. Because miglitol is excreted primarily by the kidneys, accumulation of miglitol is expected in patients with renal impairment. Patients with creatinine clearance < 25 mL/min taking 25 mg 3 times daily exhibited a greater than two-fold increase in miglitol plasma levels as compared to subjects with creatinine clearance > 60 mL/min. Dosage adjustment to correct the increased plasma concentrations is not feasible because miglitol acts locally. Little information is available on the safety of miglitol in patients with creatinine clearance < 25 mL/min.

Hepatic impairment. Miglitol pharmacokinetics were not altered in cirrhotic patients relative to healthy control subjects. Since miglitol is not metabolized, no influence of hepatic function on the kinetics of miglitol is expected.

Elderly. The pharmacokinetics of miglitol were studied in elderly and young males (n = 8 per group). At a dosage of 100 mg 3 times daily for 3 days, no differences between the two groups were found.

Gender. No significant difference in the pharmacokinetics of miglitol was observed between elderly men and women when body weight was taken into account.

Race. Several pharmacokinetic studies were conducted in Japanese volunteers, with results similar to those observed in Caucasians. A study comparing the pharmacodynamic response to a single 50-mg dose in Black and Caucasian healthy volunteers indicated similar glucose and insulin responses in both populations.

CLINICAL TRIALS

Clinical Experience in Non-Insulin-Dependent Diabetes Mellitus (NIDDM) Patients on Dietary Treatment Only: GLYSET was evaluated in two US and three non-US controlled, fixed-dose, monotherapy studies, in which 735 GLYSET-treated patients were evaluated for efficacy analyses. (See Table 1)

In Study 1, a one-year study in which GLYSET was evaluated as monotherapy and also as combination therapy, there was a statistically significantly smaller increase in mean glycosylated hemoglobin (HbA1c) over time in the miglitol 50 mg 3 times daily monotherapy arm compared to placebo. Significant reductions in mean fasting and postprandial plasma glucose levels and in mean postprandial insulin levels were observed in GLYSET-treated patients compared with the placebo group.

In Study 2, a 14-week study, there was a significant decrease in HbA1c in patients receiving GLYSET 50 mg 3 times daily or 100 mg 3 times daily compared to placebo. In addition, there were significant reductions in postprandial plasma glucose and postprandial serum insulin levels compared to placebo.

Study 3 was a 6-month dose-ranging trial evaluating GLYSET at doses from 25 mg 3 times daily to 200 mg 3 times daily. GLYSET produced a greater reduction in HbA1c than placebo at all doses, although the effect was statistically significant only at the 100 mg 3 times daily and 200 mg 3 times daily doses. In addition, all doses of GLYSET produced significant reductions in postprandial plasma glucose and postprandial insulin levels compared to placebo.

Studies 4 and 5 were 6-month studies evaluating 50 and 100 mg 3 times daily, and 100 mg 3 times daily, respectively. As compared to placebo, GLYSET produced significant reductions in HbA1c, as well as a significant reduction in postprandial plasma glucose in both studies at the doses employed.

Table 1

GLYSET Monotherapy Study Results

Study	Treatment	HbA1c (%)		1-hour Postprandial Glucose (mg/dL)	
		Mean Change from Baseline*	Treatment Effect**	Mean Change from Baseline	Treatment Effect**
1 (US)	Placebo	+0.71	—	+24	—
	GLYSET 50 mg t.i.d.***	+0.13	-0.58†	-39	-63†
2 (US)	Placebo	+0.47	—	+15	—
	GLYSET 50 mg t.i.d.	-0.22	-0.69†	-52	-67†
	GLYSET 100 mg t.i.d.	-0.28	-0.75†	-59	-74†
3 (non-US)	Placebo	+0.18	—	+2	—
	GLYSET 25 mg t.i.d.	-0.08	-0.26	-33	-35†
	GLYSET 50 mg t.i.d.	-0.22	-0.40	-45	-47†
	GLYSET 100 mg t.i.d.	-0.63	-0.81†	-62	-64†
	GLYSET 200 mg t.i.d.‡	-0.84	-1.02†	-85	-87†
4 (non-US)	Placebo	+0.01	—	+8	—
	GLYSET 50 mg t.i.d.	-0.35	-0.36†	-20	-28†
	GLYSET 100 mg t.i.d.	-0.57	-0.58†	-25	-33†
5 (non-US)	Placebo	+0.32	—	+17	—
	GLYSET 100 mg t.i.d.	-0.43	-0.75†	-38	-55†

* Mean baseline ranged from 7.54 to 8.72 % in these studies.
** The result of subtracting the placebo group average.
*** t.i.d. = 3 times daily
† $p \leq 0.05$
‡ Although results for the 200 mg 3 times daily are presented for completeness, the maximum recommended dosage of Glyset is 100 mg 3 times daily

Clinical Experience in NIDDM Patients Receiving Sulfonylureas: GLYSET was studied as adjunctive therapy to a background of maximal or near-maximal sulfonylurea (SFU) treatment in three large, double-blind, randomized studies (two US and one non-US) in which 471 GLYSET-treated patients were evaluated for efficacy.(See Table 2)

Study 6 included patients under treatment with maximal doses of SFU at entry. At the end of this 14-week study, the mean treatment effects on glycosylated hemoglobin (HbA1c) were -0.82% and -0.74% for patients receiving GLYSET 50 mg 3 times daily +SFU and GLYSET 100 mg 3 times daily +SFU, respectively.

Study 7 was a one-year study in which GLYSET at 25, 50 or 100 mg 3 times daily was added to a maximal dose of glyburide (10 mg twice daily). At the end of this study, the mean treatment effects on HbA1c of GLYSET when added to maximum glyburide therapy were -0.30%, -0.62%, and -0.73% with the 25, 50 and 100 mg 3 times daily GLYSET dosages, respectively.

In Study 8, the addition of GLYSET 100 mg 3 times daily to a background of treatment with glyburide produced an additional mean treatment effect on HbA1c of -0.66 %.

Table 2

GLYSET Plus Sulfonylurea (SFU) Combination Therapy Results

Study	Treatment	HbA1c (%)		1-hour Postprandial Glucose (mg/dL)	
		Mean Change from Baseline*	Treatment Effect**	Mean Change from Baseline	Treatment Effect**
6 (US)	Placebo + SFU	+0.33	—	-1	—
	GLYSET 50 mg t.i.d.*** + SFU	-0.49	-0.82†	-69	-68†
	GLYSET 100 mg t.i.d. + SFU	-0.41	-0.74†	-73	-72†
7 (US)	Placebo + SFU	+1.01	—	48	—
	GLYSET 25 mg t.i.d. + SFU	+0.71	-0.30†	-2	-50†
	GLYSET 50 mg t.i.d. + SFU	+0.39	-0.62†	-13	-61†
	GLYSET 100 mg t.i.d. + SFU	+0.28	-0.73†	-33	-81†
8 (non-US)	Placebo + SFU	+0.16	—	+10	—
	GLYSET 100 mg t.i.d. + SFU	-0.50	-0.66†	-36	-46†

* Mean baseline ranged from 8.56 to 9.16 % in these studies.

** The result of subtracting the placebo group average.

*** t.i.d. = 3 times daily

† $p \leq 0.05$

Dose-Response: Results from controlled, fixed-dose studies of GLYSET as monotherapy or as combination treatment with a sulfonylurea were combined to derive a pooled estimate of the difference from placebo in the mean change from baseline in glycosylated hemoglobin (HbA1c) and postprandial plasma glucose as shown in Figures 1 and 2:

Figure 1

HbA1c (%)
Mean Change From Baseline: Treatment Effect
Pooled Results from Controlled Fixed-Dose Studies in Tables 1 and 2

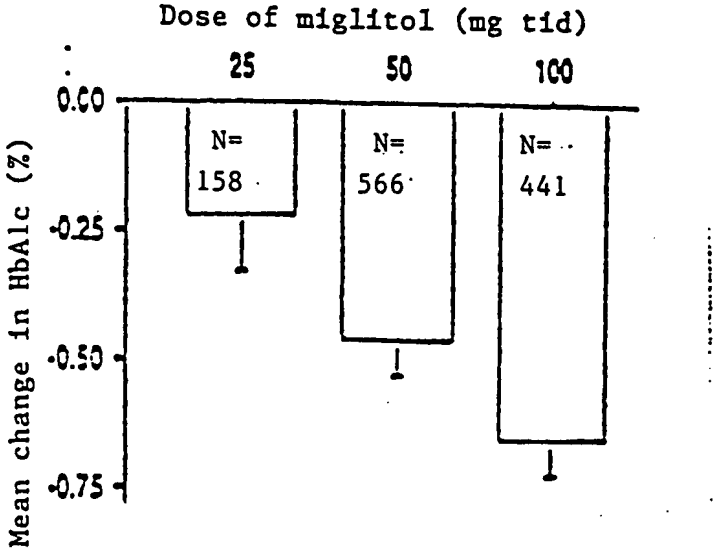
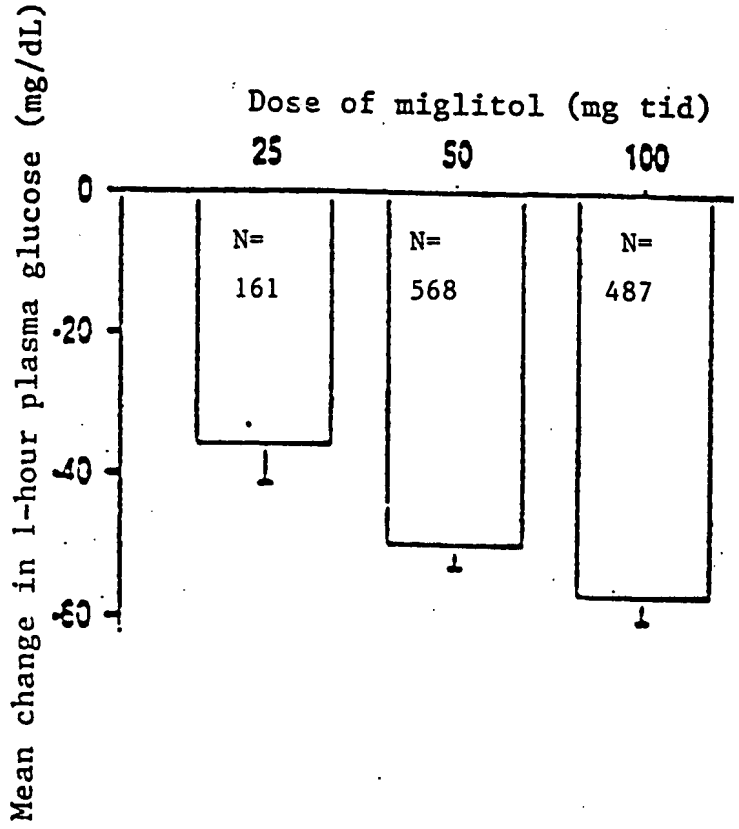


Figure 2

1- Hour Postprandial Plasma Glucose
Mean Change From Baseline:Treatment Effect
Pooled Results from Controlled Fixed-Dose Studies in Tables 1 and 2



Because of its mechanism of action, the primary pharmacologic effect of miglitol is manifested as a reduction in postprandial plasma glucose, as shown previously in all of the major clinical trials. GLYSET was statistically significantly different from placebo at all doses in each of the individual studies with respect to effect on mean one-hour postprandial plasma glucose, and there is a dose response from 25 to 100 mg 3 times daily for this efficacy parameter.

INDICATIONS AND USAGE

GLYSET, as monotherapy, is indicated as an adjunct to diet to improve glycemic control in patients with non-insulin-dependent diabetes mellitus (NIDDM) whose hyperglycemia cannot be managed with diet alone. GLYSET may also be used in combination with a sulfonylurea when diet plus either GLYSET or a sulfonylurea alone do not result in adequate glycemic control. The effect of GLYSET to enhance glycemic control is additive to that of sulfonylureas when used in combination, presumably because its mechanism of action is different.

In initiating treatment for NIDDM, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling blood glucose and symptoms of hyperglycemia. The importance of regular physical activity when appropriate should also be stressed. If this treatment program fails to result in adequate glycemic control, the use of GLYSET should be considered. The use of GLYSET must be viewed by both the physician and patient as a treatment in addition to diet and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint.

CONTRAINDICATIONS

GLYSET is contraindicated in patients with:

- Diabetic ketoacidosis
- Inflammatory bowel disease, colonic ulceration, or partial intestinal obstruction and in patients predisposed to intestinal obstruction
- Chronic intestinal diseases associated with marked disorders of digestion or absorption or with conditions that may deteriorate as a result of increased gas formation in the intestine
- Hypersensitivity to the drug or any of its components

PRECAUTIONS

General

Hypoglycemia: Because of its mechanism of action, GLYSET when administered alone should not cause hypoglycemia in the fasted or postprandial state. Sulfonylurea agents may cause hypoglycemia. Because GLYSET given in combination with a sulfonylurea will cause a further lowering of blood glucose, it may increase the hypoglycemic potential of the sulfonylurea, although this was not observed in clinical trials. Oral glucose (dextrose), whose absorption is not delayed by GLYSET, should be used instead of sucrose (cane sugar) in the treatment of mild-to-moderate hypoglycemia. Sucrose, whose hydrolysis to glucose and fructose is inhibited by GLYSET, is unsuitable for the rapid correction of hypoglycemia. Severe hypoglycemia may require the use of either intravenous glucose infusion or glucagon injection.

Loss of Control of Blood Glucose: When diabetic patients are exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of control of blood glucose may occur. At such times, temporary insulin therapy may be necessary.

Renal Impairment: Plasma concentrations of GLYSET in renally impaired volunteers were proportionally increased relative to the degree of renal dysfunction. Long-term clinical trials in diabetic patients with significant renal dysfunction (serum creatinine >2.0 mg/dL) have not been conducted. Therefore, treatment of these patients with GLYSET is not recommended.

Information for Patients: the following information should be provided to patients:

- GLYSET should be taken orally three times a day at the start (with the first bite) of each main meal. It is important to continue to adhere to dietary instructions, a regular exercise program, and regular testing of urine and/or blood glucose.

- GLYSET itself does not cause hypoglycemia even when administered to patients in the fasted state. Sulfonylurea drugs and insulin, however, can lower blood sugar levels enough to cause symptoms or sometimes life-threatening hypoglycemia. Because GLYSET given in combination with a sulfonylurea or insulin will cause a further lowering of blood sugar, it may increase the hypoglycemic potential of these agents. The risk of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be well understood by patients and responsible family members. Because GLYSET prevents the breakdown of table sugar, a source of glucose (dextrose, D-glucose) should be readily available to treat symptoms of low blood sugar when taking GLYSET in combination with a sulfonylurea or insulin.

- If side effects occur with GLYSET, they usually develop during the first few weeks of therapy. They are most commonly mild-to-moderate dose-related gastrointestinal effects, such as flatulence, soft stools, diarrhea, or abdominal discomfort, and they generally diminish in frequency and intensity with time. Discontinuation of drug usually results in rapid resolution of these gastrointestinal symptoms.

Laboratory Tests: Therapeutic response to GLYSET may be monitored by periodic blood glucose tests. Measurement of glycosylated hemoglobin levels is recommended for the monitoring of long-term glycemic control.

Drug Interactions: Several studies investigated the possible interaction between miglitol and glyburide. In six healthy volunteers given a single dose of 5-mg glyburide on a background of 6 days treatment with miglitol (50 mg 3 times daily for 4 days followed by 100 mg 3 times daily for 2 days) or placebo, the mean C_{max} and AUC values for glyburide were 17% and 25% lower, respectively, when glyburide was given with miglitol. In a study in diabetic patients in which the effects of adding miglitol 100 mg 3 times daily x 7 days or placebo to a background regimen of 3.5 mg glyburide daily were investigated, the mean AUC value for glyburide was 18% lower in the miglitol-treated group, although this difference was not statistically significant. Further information on a potential interaction with glyburide was obtained from one of the large US clinical trials (Study 7) in which patients were dosed with either miglitol or placebo on a background of glyburide 10 mg twice daily. At the 6-month and 1-year clinic visits, patients taking concomitant miglitol 100 mg 3 times daily exhibited mean C_{max} values for glyburide that were 16% and 8% lower, respectively, compared to patients taking glyburide alone. However, these differences were not statistically significant. Thus, although there was a trend toward lower AUC and C_{max} values for glyburide when co-administered with GLYSET, no definitive statement regarding a potential interaction can be made based on the foregoing three studies.

The effect of miglitol (100 mg 3 times daily x 7 days) on the pharmacokinetics of a single 1000-mg dose of metformin was investigated in healthy volunteers. Mean AUC and C_{max} values for metformin were 12% to 13% lower when the volunteers were given miglitol as compared with placebo, but this difference was not statistically significant.

In a healthy volunteer study, co-administration of either 50 mg or 100 mg miglitol 3 times daily together with digoxin reduced the average plasma concentrations of digoxin by 19% and 28%, respectively. However, in diabetic patients under treatment with digoxin, plasma digoxin concentrations were not altered by co-administration of miglitol 100 mg 3 times daily x 14 days.

Other healthy volunteer studies have demonstrated that miglitol may significantly reduce the bioavailability of ranitidine and propranolol by 60% and 40%, respectively. No effect of miglitol was observed on the pharmacokinetics or pharmacodynamics of either warfarin or nifedipine.

Intestinal adsorbents (e.g., charcoal) and digestive enzyme preparations containing carbohydrate-splitting enzymes (e.g., amylase, pancreatin) may reduce the effect of GLYSET and should not be taken concomitantly.

In 12 healthy males, concomitantly administered antacid did not influence the pharmacokinetics of miglitol.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Miglitol was administered to mice by the dietary route at doses as high as approximately 500 mg/kg body weight (corresponding to greater than 5 times the exposure in humans based on AUC) for 21 months. In a two-year rat study, miglitol was administered in the diet at exposures comparable to the maximum human exposures based on AUC. There was no evidence of carcinogenicity resulting from dietary treatment with miglitol.

In vitro, miglitol was found to be non-mutagenic in the bacterial mutagenesis (Ames) assay and the eukaryotic forward mutation assay (CHO/HGPRT). Miglitol did not have any clastogenic effects *in vivo* in the mouse micronucleus test. There were no heritable mutations detected in dominant lethal assay.

A combined male and female fertility study conducted in Wistar rats treated orally with miglitol at dose levels of 300 mg/kg body weight (approximately 8 time the maximum human exposure based on body surface area) produced no untoward effect on reproductive performance or capability to reproduce. In addition, survival, growth, development, and fertility of the offspring were not compromised.

Pregnancy:

Teratogenic Effects: Pregnancy Category B. The safety of GLYSET in pregnant women has not been established. Developmental toxicology studies have been performed in rats at doses of 50, 150 and 450 mg/kg, corresponding to levels of approximately 1.5, 4, and 12 times the maximum recommended human exposure based on body surface area. In rabbits, doses of 10, 45, and 200 mg/kg corresponding to levels of approximately 0.5, 3, and 10 times the human exposure were examined. These studies revealed no evidence of fetal malformations attributable to GLYSET. Doses of GLYSET up to 4 and 3 times the human dose (based on body surface area), for rats and rabbits, respectively, did not reveal evidence of impaired fertility or harm to the fetus. The highest doses tested in these studies, 450 mg/kg in the rat and 200 mg/kg in the rabbit promoted maternal and/or fetal toxicity. Fetotoxicity was indicated by a slight but significant reduction in fetal weight in the rat study and slight reduction in fetal weight, delayed ossification of the fetal skeleton and increase in the percentage of non-viable fetuses in the rabbit study. In the peri-postnatal study in rats, the NOAEL (No Observed Adverse Effect Level) was 100 mg/kg (corresponding to approximately four times the exposure to humans, based on body surface area). An increase in stillborn progeny was noted at the high dose (300 mg/kg) in the rat peri-postnatal study, but not at the high dose (450 mg/kg) in the delivery segment of the rat developmental toxicity study. Otherwise, there was no adverse effect on survival, growth, development, behavior, or fertility in either the rat developmental toxicity or peri-postnatal studies. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Miglitol has been shown to be excreted in human milk to a very small degree. Total excretion into milk accounted for 0.02% of a 100-mg maternal dose. The estimated exposure to a nursing infant is approximately 0.4% of the maternal dose. Although the levels of miglitol reached in human milk are exceedingly low, it is recommended that GLYSET not be administered to a nursing woman.

Pediatric Use: Safety and effectiveness of GLYSET in pediatric patients have not been established.

ADVERSE REACTIONS

Gastrointestinal: Gastrointestinal symptoms are the most common reactions to GLYSET. In U.S. placebo-controlled trials, the incidences of abdominal pain, diarrhea, and flatulence were 11.7%, 28.7%, and 41.5% respectively in 962 patients treated with miglitol 25-100 mg 3 times daily, whereas the corresponding incidences were 4.7%,10.0%, and 12.0% in 603 placebo-treated patients. The incidence of diarrhea and abdominal pain tended to diminish considerably with continued treatment.

Dermatologic: Skin rash was reported in 4.3% of miglitol-treated patients compared to 2.4% of placebo-treated patients. Rashes were generally transient and most were assessed as unrelated to GLYSET by physician-investigators.

Abnormal Laboratory Findings: Low serum iron occurred more often in GLYSET-treated patients (9.2%) than in placebo-treated patients (4.2%) but did not persist in the majority of cases and was not associated with reductions in hemoglobin or changes in other hematologic indices.

OVERDOSAGE

Unlike sulfonylureas or insulin, an overdose of GLYSET will not result in hypoglycemia. An overdose may result in transient increases in flatulence, diarrhea, and abdominal discomfort. Because of the lack of extra-intestinal effects seen with GLYSET, no serious systemic reactions are expected in the event of an overdose.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with GLYSET or any other pharmacologic agent. Dosage of GLYSET must be individualized on the basis of both effectiveness and tolerance while not exceeding the maximum recommended dosage of 100 mg 3 times daily GLYSET should be taken three times daily at the start (with the first bite) of each main meal. GLYSET should be started at 25 mg, and the dosage gradually increased as described below, both to reduce gastrointestinal adverse effects and to permit identification of the minimum dose required for adequate glycemic control of the patient.

During treatment initiation and dose titration (see below), one-hour postprandial plasma glucose may be used to determine the therapeutic response to GLYSET and identify the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin should be measured at intervals of approximately three months. The therapeutic goal should be to decrease both postprandial plasma glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dose of GLYSET, either as monotherapy or in combination with a sulfonylurea.

Initial Dosage: The recommended starting dosage of GLYSET is 25 mg, given orally three times daily at the start (with the first bite) of each main meal. However, some patients may benefit by starting at 25 mg once daily to minimize gastrointestinal adverse effects, and gradually increasing the frequency of administration to 3 times daily.

Maintenance Dosage: The usual maintenance dose of GLYSET is 50 mg 3 times daily, although some patients may benefit from increasing the dose to 100 mg 3 times daily. In order to allow adaptation to potential gastrointestinal adverse effects,it is recommended that GLYSET therapy be initiated at a dosage of 25 mg 3 times daily, the lowest effective dosage, and then gradually titrated upward to allow adaptation. After 4 - 8 weeks of the 25 mg 3 times daily regimen, the dosage should be increased to 50 mg 3 times daily for approximately three months, following which a glycosylated hemoglobin level should be measured to assess therapeutic response. If, at that time, the glycosylated hemoglobin level is not satisfactory, the dosage may be further increased to 100 mg 3 times daily, the maximum recommended dosage. Pooled data from controlled studies suggest a dose-response for both HbA1c and one-hour postprandial plasma glucose throughout the recommended dosage range. However, no single study has examined the effect on glycemic control of titrating patients' doses upwards within the same study. If no further reduction in postprandial glucose or glycosylated hemoglobin levels is observed with titration to 100 mg 3 times daily, consideration should be given to lowering the dose. Once an effective and tolerated dosage is established, it should be maintained.

Maximum Dosage: The maximum recommended dosage of GLYSET is 100 mg 3 times daily. In one clinical trial, 200 mg 3 times daily gave additional improved glycemic control but increased the incidence of the gastrointestinal symptoms described above.

Patients Receiving Sulfonylureas: Sulfonylurea agents may cause hypoglycemia. There was no increased incidence of hypoglycemia in patients who took GLYSET in combination with sulfonylurea agents compared to the incidence of hypoglycemia in patients receiving sulfonylureas alone in any clinical trial. However, GLYSET given in combination with a sulfonylurea will cause a further lowering of blood glucose and may increase the risk of hypoglycemia due to the additive effects of the two agents. If hypoglycemia occurs, appropriate adjustments in the dosage of these agents should be made.

HOW SUPPLIED

GLYSET is available as 25-mg, 50-mg, and 100-mg light-gray, hexagonal-shaped, film-coated tablets. The 25-mg tablet is debossed with the word "GLYSET" on one side and "25" on the other. The 50-mg tablet is debossed with the word "GLYSET" on one side and "50" on the other. The 100-mg tablet is debossed with the word "GLYSET" on one side and "100" on the other.

	Strength	NDC	Tablet Identification Front	Back
Bottles of 100:	25 mg	0026-2871-51	GLYSET	25
	50 mg	0026-2872-51	GLYSET	50
	100 mg	0026-2873-51	GLYSET	100
Bottles of 1000:	25 mg	0026-2871-54	GLYSET	25
	50 mg	0026-2872-54	GLYSET	50
	100 mg	0026-2873-54	GLYSET	100
Unit Dose Packages of 100:	25 mg	0026-2871-48	GLYSET	25
	50 mg	0026-2872-48	GLYSET	50
	100 mg	0026-2873-48	GLYSET	100

Store between 15°-30°C (59°-86°F). For bottles, keep container tightly closed.

Caution: Federal law prohibits dispensing without a prescription.

Bayer Corporation
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West Haven, CT 06516 USA

United States Patent [19]

Junge et al.

[11] **Patent Number: 4,639,436**

[45] **Date of Patent: Jan. 27, 1987**

[54] **ANTIDIABETIC 3,4,5-TRIHYDROXYPIPERIDINES**

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[73] Assignee: **Bayer Aktiengesellschaft, Leverkusen, Fed. Rep. of Germany**

[21] Appl. No.: **936,280**

[22] Filed: **Aug. 23, 1978**

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Dec. 24, 1977 [DE] Fed. Rep. of Germany 27580252

[51] Int. Cl.[4] A61K 31/70; C07D 211/46

[52] U.S. Cl. 514/24; 514/32; 514/42; 514/222; 514/226; 514/236; 514/241; 514/252; 514/256; 514/318; 514/326; 514/328; 536/17.4; 536/18.7; 536/23; 544/55; 544/58.6; 544/63; 544/96; 544/98; 544/216; 544/238; 544/332; 544/406; 546/116; 546/213; 546/214; 546/193; 546/219; 546/220; 546/194; 546/242; 546/243; 546/197; 546/200; 546/201; 546/208; 546/209; 546/212

[58] Field of Search 546/242, 243, 219, 220, 546/193, 212, 194, 213, 209, 214; 424/267; 514/328, 222, 226, 236, 241, 318, 326, 252, 256, 24, 32, 42; 536/17.4, 18.7, 23; 544/55, 58.6, 63, 96, 98, 216, 238, 332, 406

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Primary Examiner—Richard A. Schwartz
Attorney, Agent, or Firm—Sprung Horn Kramer & Woods

[57] **ABSTRACT**

The invention includes certain 3,4,5-trihydroxypiperidine compounds, methods for their preparation, compositions containing said 3,4,5-trihydroxypiperidine compounds and methods for the use of said compounds and compositions.

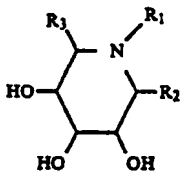
The subject matter of the invention is useful against diabetes, hyperlipaemia and adiposity as well as in animal nutrition.

32 Claims, No Drawings

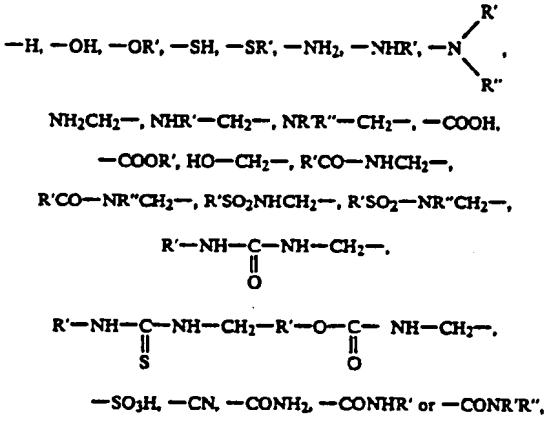
ANTIDIABETIC 3,4,5-TRIHYDROXYPIPERIDINES

The present invention relates to certain new 3,4,5-trihydroxypiperidine compounds, to several processes for their production and to their use as medicaments, in particular as agents against diabetes, hyperlipaemia and adiposity, and in animal nutrition, for influencing the lean meat/fat ratio in favour of the proportion of lean meat.

The present invention provides compounds which are 3,4,5-trihydroxypiperidines of the following general formula or their pharmaceutically acceptable salts and bioprecursors:



in which R_1 and R_3 are the same or different and each is H or an optionally substituted, straight-chain, branched or cyclic saturated or unsaturated aliphatic hydrocarbon radical e.g. alkyl, alkenyl or alkinyl or an optionally substituted carbocyclic aromatic or heterocyclic radical and R_2 is



—H, —OH, —OR', —SH, —SR', —NH_2, —NHR', —N(R')(R"),

NH_2CH_2—, NHR'—CH_2—, NR'R"—CH_2—, —COOH,

—COOR', HO—CH_2—, R'CO—$NHCH_2$—,

R'CO—NR"CH_2—, R'SO_2NHCH_2—, R'SO_2—NR"CH_2—,

R'—NH—C(=O)—NH—CH_2—,

R'—NH—C(=S)—NH—CH_2—R'—O—C(=O)— NH—CH_2—,

—SO_3H, —CN, —$CONH_2$, —CONHR' or —CONR'R",

wherein R' and R" are the same or different and each has any of the meanings given above for R_1, provided that when R_3 is —CH_2OH and R_2 is H or OH; RHD 3 is H and R_2 is H, OH, SO_3H, —CN or CH_2—NH_2; or R_3 is —CH_2—NH_2 and R_2 is OH, then R_1 is not H. R_3 preferably is —H, —CH_3, —CH_2OH, —CH_2—NH_2, NHR'—CH_2—, NR'R"—CH_2—, R'CONH—CH_2—, R'CO—NR"CH_2—, Hal—CH_2—, R'O—CH_2—, R'$COOCH_2$—, R'SO_2O—CH_2—, R'SO_2NHCH_2—, R'SO_2—NR"CH_2—, R'NH—CO—NH—CH_2—, R'NHCS—NH—CH_2—, R'O—CO—NH—CH_2—, —CN, —COOH, —COOR', —$CONH_2$, —CONHR' or —CONR'R", wherein R' and R" are the same or different and each has any of the meanings given above for R_1.

For the purpose of this specification the term 'pharmaceutically acceptable bioprecursor' of an active compound of the invention means a compound having a structural formula different from the active compound but which nonetheless, upon administration to a warm-blooded animal is converted in the patient's body to the active compound.

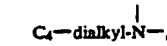
Suitable pharmaceutical acceptable salts are e.g. chlorides, sulfates, acetates, carbonates and oxalates.

R_1, R' and R" are the same or different and preferably each is alkyl having from 1 to 30, desirably from 1 to 18, and more desirably from 1 to 10 C atoms, alkenyl or alkinyl having from 2 to 18, desirably from 3 to 10, C atoms, a monocyclic, bicyclic or tricyclic aliphatic radical having from 3 to 10 C atoms, which can be saturated, mono-unsaturated or di-unsaturated, carbocyclic particularly cycloalkyl, cycloalkenyl or cycloalkinyl having 3 to 8 carbon atoms, such as cyclopentyl, cyclohexyl, cyclopentenyl, cyclohexenyl, cyclopentadienyl or cyclohexadienyl aryl having 6 or 10 C atoms, such as phenyl or naphthyl, or a heterocyclic radical having from 3 to 8, in particular from 3 to 6, ring members which can contain 1, 2, 3 or 4 hetero-atoms, each of which is preferably N, O or S, and to which a benzene ring or a further said heterocyclic radical can be fused, each of the above groups being optionally substituted by from i to 5, most preferably by 1, 2 or 3, substituents.

Examples which may be mentioned of substituents for alkyl are: hydroxyl, and alkoxy having preferably from 1 to 4 carbon atoms, in particular methoxy and ethoxy; acyloxy, the acyl radical being derived from an aliphatic (particularly alkane) carboxylic acid having from 1 to 7 C atoms, an aromatic carboxylic acid, most preferably a phenyl-carboxylic acid, such as benzoic acid, phthalic acid, etc, optionally substituted in the phenyl moiety by one, two or more of —OH, -halogen, preferably F, Cl or Br, C_1 to C_4-alkyl, C_1 to C_4-alkoxy, nitr and/or amino, or a heterocyclic carboxylic acid which is derived from a 5-membered or 6-membered heterocyclic compound containing from 1 to 3 hetero-atoms each of which is N, O or S and optionally substituted in the heterocyclic ring moiety by C_1 to C_4-alkyl, chlorine, bromine or amino; amino, monoalkylamino and dialkylamino having preferably from 1 to 4 carbon atoms in each alkyl moiety, most preferably monomethylamino, monoethylamino, dimethylamino and diethylamino, and monoacylamino, the acyl moiety being derived from an aliphatic (particularly alkane) carboxylic acid having from 1 to 7 C atoms, an aromatic carboxylic acid, most preferably a phenyl-carboxylic acid, such as benzoic acid, phthalic acid, etc., optionally substituted in the phenyl moiety by —OH, -halogen, most preferably F, Cl or Br, C_1 to C_4-alkyl, C_1 to C_4-alkoxy, nitro and/or amino, or a heterocyclic carboxylic acid which is derived from a 5-membered or 6-membered heterocyclic compound containing from 1 to 3 hetero-atoms each of which is N, O or S and optionally substituted in the heterocyclic ring moiety by C_1 to C_4-alkyl, chlorine, bromine or amino; mercapto, or alkylthio having preferably from 1 to 4 carbon atoms, in particular methylthio or ethylthio; halogen, preferably fluorine, chlorine or bromine; alkylcarbonyl having preferably from 1 to 4 carbon atoms in the alkyl moiety; carboxyl, nitro, cyano, an aldehyde group or a sulphonic acid group; or a heterocyclic radical of the above mentioned type, or most preferably, a heterocyclic radical which is derived from a sugar, preferentially from a hexose or pentose, which can be bonded to the alkyl moiety directly via a ring atom or via an —O—, —S— or an —NH—bridge.

Examples of heterocyclic substituents of the alkyl are: phthalimido, pyridyl, thienyl, furyl, isoxazolyl,

thiazolyl, glucopyranosyl, ribofuranosyl, oxiranyl and the like. Further suitable substituents of the alkyl are aromatic radicals, such as naphthyl and in particular phenyl, optionally having one or more, preferably from 1 to 3, identical or different substituents each of which is —OH, —NH_2, C_1 to C_4-alkyl-NH—, C_1 to



C_1 to C_4-alkoxy, NO_2, —CN, —COOH, —COO-alkyl (C_1 to C_4), C_1 to C_6-alkyl, halogen, most preferably fluorine, chlorine or bromine, C_1 to C_4-alkylthio, —SH, C_1 to C_4-alkylsulphonyl, —SO_3H, —S_2-NH_2 and —SO_2-NH-alkyl (C_1 to C_4).

The alkyl can also have a monocyclic, bicyclic or tricyclic aliphatic substituent having preferably from 3 to 10 carbon atoms, which in turn can be substituted by hydroxyl, amino, halogen, most preferably fluorine, chlorine or bromine, or —COOH.

The alkyl preferably is substituted by hydroxyl, alkoxy from 1 to 4 carbon atoms, mercapto, alkylthio, having from 1 to 4 carbon atoms, halogen, nitro, amino, monoalkylamino having from 1 to 4 C atoms and acylamino, the acyl moiety being derived from an aliphatic carboxylic acid having from 1 to 6 C atoms.

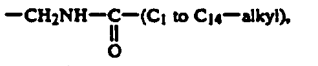
Possible substituents for the monocyclic, bicyclic or tricyclic radicals R_1, R' and R" are the substituents quoted hereinabove for alkyl.

The aryl radicals can have one or more, preferably from 1 to 3, identical or different substituents. Examples of substituents which may be mentioned are: alkyl having from 1 to 10 C atoms, which can in turn themselves be substituted, for example by chlorine, nitro or cyano; optionally substituted alkenyl having from 1 to 10 carbon atoms; hydroxyl, alkoxy having preferably from 1 to 4 carbon atoms; amino and monoalkylamino and di-alkylamino having preferably from 1 to 4 carbon atoms per alkyl moiety; mercapto, and alkylthio having preferably from 1 to 4 carbon atoms; carboxyl, carbalkoxy having preferably from 1 to 4 carbon atoms, the sulphonic acid group, alkylsulphonyl having preferably from 1 to 4 carbon atoms and arylsulphonyl, preferably phenylsulphonyl; aminosulphonyl, and alkylaminosulphonyl and dialkylaminosulphonyl having from 1 to 4 carbon atoms per alkyl moiety, preferably methylaminosulphonyl and dimethylaminosulphonyl; nitro, cyano or the aldehyde group; alkylcarbonylamino having preferably from 1 to 4 carbon atoms; and alkylcarbonyl having from 1 to 4 carbon atoms, benzoyl, benzylcarbonyl and phenylethylcarbonyl, the last-mentioned alkyl, phenyl, benzyl and phenylethyl being in turn themselves optionally substituted, for example by chlorine, nitro or hydroxyl.

The heterocyclic radicals R_1 are preferably derived from hetero-paraffinic, hetero-aromatic or hetero-olefinic 5-membered or 6-membered rings having preferably from 1 to 3 identical or different hetero-atoms, each of which is oxygen, sulphur or nitrogen. These ring systems can carry further substituents, such as, for example, hydroxyl, amino or C_1 to C_4-alkyl, or benzene or other, preferably 6-membered, heterocyclic rings of the type mentioned hereinabove can be fused to them.

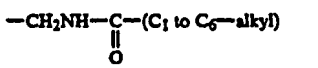
Particularly preferred heterocyclic radicals are derived, for example, from furane, pyrane, pyrrolidine, piperidine, pyrazole, imidazole, pyrimidine, pyridazine, pyrazine, triazine, pyrrole, pyridine, benzimidazole, quinoline, isoquinoline or purine.

In the compounds of the formula I, R_2 preferably represents —H, —OH, —SO_3H, —CN, —CH_2NH_2, —CH_2NH—(C_1 to C_{14}-alkyl),



—CH_2—NH—SO_2(C_1 to C_{14})-alkyl or —CH_2—NH—SO_2-phenyl. R_2 very particularly preferably represents —H, —SO_3H or —CN.

R_3 preferably represents hydrogen, —CH_2—OH, —CH_3, —CH_2NH_2, —CH_2NH—(C_1 to C_6-alkyl),



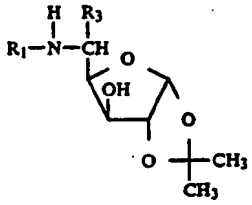
or —CH_2—O—(C_1–C_6-alkyl). However, R_3 very particularly preferably represents —CH_2OH.

It has been found that the new compounds of the formula I are potent inhibitors for α-glucosidases, in particular for disaccharidases. The new compounds are thus valuable agents for influencing a member of metabolic processes and thus constitute an enrichment of pharmacy.

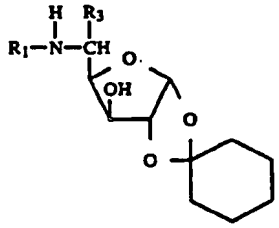
Furthermore the compounds of the formula I, especially those with R_1=C_6 to C_{10}-n-alkyl are inhibitors for the triglycerid and cholesterol absorption.

Compared with 2-hydroxymethyl-3,4,5-trihydroxypiperidine, which is known from DT-OS (German Published Specification) No. 2,656,602, the new compounds have advantageous therapeutic properties.

The present invention further provides a process for the production of a compound according to the invention in which a compound of the general formula II or IIa



II



IIa

in which R_1 and R_3 have the same meaning as defined hereinbefore in formula I, is subjected to acid hydrolysis so as to remove the isopropylidene or cyclohexylidene protective group, it sometimes being advantageous to isolate the compound of the formula I in the form of an adduct of sulphurous acid or of hydrocyanic acid (R_2=SO_3H or CN). The compounds of the formula I in which R_2 is OH can be liberated from the bisulphite addition products by treatment with bases, preferably

alkaline earth metal hydroxides, such as $Ca(OH)_2$ or $Sr(OH)_2$, but most preferably $Ba(OH)_2$. The compounds of the formula I in which R_2 is H can be obtained from compounds of the formula I in which R_2 is OH by reaction with hydrogen donor reducing agents, such as, for example, $NaBH_4$.

Furthermore, it has been found that a compound of the formula I can be obtained when a compound of the formula I in which R_2 is OH is reacted with hydrocyanic acid in a manner which is in itself known so as to produce a compound of the formula I in which R_2 is CN, and a compound in which R_2 is $—CH_2NH_2$ is optionally obtained from the products by catalytic hydrogenation of the nitrile group, and the amino group is optionally acylated, alkylated or sulphonylated in a manner which is in itself known so as to produce a compound of the formula I in which R_2 is $R'CONCH_2—$, $R'CONR''CH_2—$, $NHR'—CH_2—$, $NR'R''—CH_2—$ or $R'SO_2NHCH_2—$, wherein R' and R'' have the same meaning as defined hereinbefore in formula I.

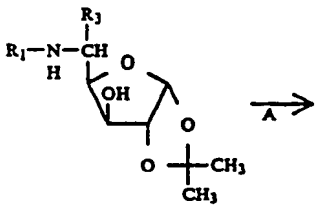
A compound of the formula I in which R_2 is —OR', —SH, —SR', $—NH_2$, —NHR' or —NR'R'' can be obtained by reacting a compound of the formula I in which R_2 is —OH with an alcohol (R'OH), H_2S, mercaptan (R'SH), ammonia or amine (H_2NR' or HNR'R''), wherein R' and R'' having the same meaning as defined hereinbefore in formula I in a manner which is in itself known.

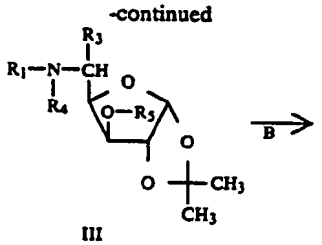
A compound of the formula I in which R_2 is —COOH may be obtained by hydrolysis of a compound of the formula I in which R_2 is —CN in a manner which is in itself known.

In a manner which is in itself known, a compound of the formula I in which R_2 is —COOR' may be obtained from the resulting carboxylic acid by reaction with an alcohol (R'OH), and a compound of the formula I in which R_2 is —CONHR' or —CONR'R'' or $—CONH_2$ may be obtained by aminolysis of a resulting ester with NH_3, $R'NH_2$ or R'R''NH, wherein R' and R'' have the same meaning as defined hereinbefore in formula I.

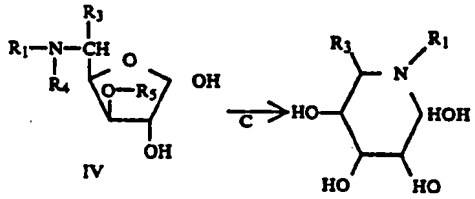
A compound of the formula I in which R_2 is —OH may also be obtained when a compound of the formula II is reacted with trifluoroacetic anhydride (reaction step A) so as to produce a compound of the formula III, the isopropylidene protective group being then split off by acid hydrolysis (reaction step B) and the trifluoroacetyl group in the compound IV is subsequently removed in a neutral to alkaline reaction medium (reaction step C).

The reaction sequence indicated may be illustrated as follows:





III



IV

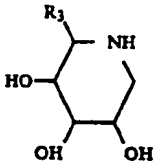
In the above formulae, R_1 and R_3 have the same meaning as defined hereinbefore in formula I, and

R_4 is trifluoroacetyl and

R_5 is trifluoroacetyl or hydrogen.

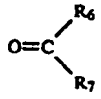
An analogous reaction sequence is applicable to the compounds of the formula IIa.

It has also been found that a compound of the formula I in which R_2 is H can be obtained when a compound of the general formula V



V

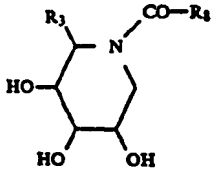
wherein R_3 has the same meaning as defined hereinbefore in formula I, is reacted with a carbonyl compound of the general formula VI



VI

in which R_6 and R_7 are the same or different and each has the same meaning as given for R_1 or R_6 and R_7 are members of an alicyclic or heterocyclic ring, in the presence of a hydrogen donor reducing agent.

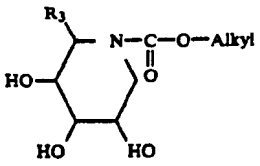
A compound of the formula I in which R_2 is H may also be obtained by reaction of: an amide of the following general formula VII or a derivative thereof with hydroxyl-protective groups



VII

in which R_3 has the same meaning as defined hereinbefore in formula I and R_8 has the same possible meanings as given for R_1 in formula I, or a carbamate of the fol-

lowing general formula VIII or a derivative thereof provided with hydroxyl-protective groups



VIII

is reduced to the corresponding amine with an amide-reducing agent.

A further process for the preparation of compounds of the formula I in which R_2 is H comprises reaction of a compound of the formula V with a reactive alkylating agent of the formula IX

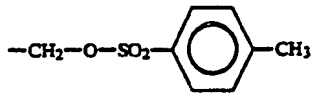
$$Z-R_1 \qquad IX$$

wherein

R_1 is alkyl having the same meaning as in formula I hereinabove and

Z is an easily eliminated leaving group, such as, for example, halide or $^{\ominus}O\text{-}SO_3H$, which is customary in alkylating agents.

In addition, in a compound of the formula I in which P_3 is $-CH_2OH$, the $-CH_2OH$ group can be selectively converted into a

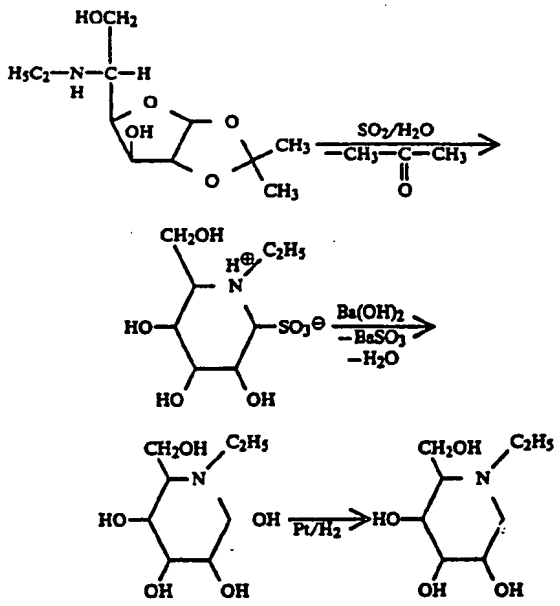


group in a manner which is in itself known and this then either converted into a $-CH_3$ group by reduction or into an amino group by reduction, via a $-CH_2-N_3$ group. Compounds of the formula I may also be obtained when, in a compound of the formula I in which R_3 is $-CH_2-NH_2$, derivatives of the amino group, are prepared by reaction with aldehydes or ketones in the presence of a hydrogen donor or with carboxylic acid chlorides or sulphonic acid chlorides, chlorocarbonic acid esters, isocyanates, isothiocyanates, and alkyl halides, in a manner which is in itself known.

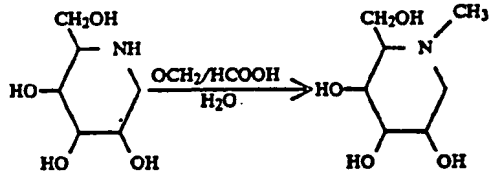
Compounds of the formula I in which R_1 is an aliphatic or aromatic radical which is substituted by an acylamino, sulphonylamino, alkoxycarbonylamino, ureido or thioureido group can be obtained starting from compounds of the formula I in which R_1 is an aliphatic or aromatic radical which is substituted by an amino group, by reacting this amino group with a carboxylic acid chloride or sulphonic acid chloride or with a chlorocarbonic acid ester, isocyanate or isothiocyanate in a manner which is in itself known.

The individual procedures for the preparation of the active compounds according to the invention are illustrated, by way of example only, below:

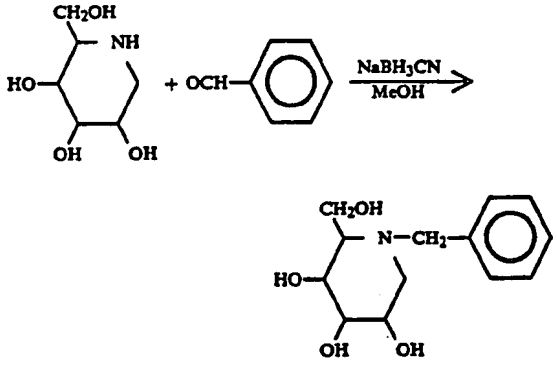
If a compound of the formula II in which R_1 is ethyl is used as a starting material, the course of a suitable reaction can be represented as follows:



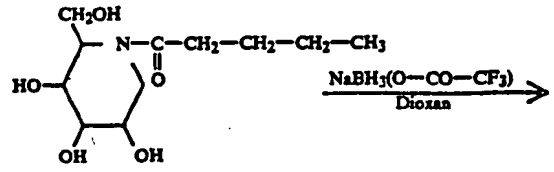
If 1-desoxynojirimycin (a compound of the general formula V) and formaldehyde are used as starting materials, a suitable reaction can be represented as follows:



If benzaldehyde is used as the carbonyl component, reductive alkylation may be carried out as follows:



If an acid amide of the general formula VII is used as starting material, a suitable reaction can be described as follows:



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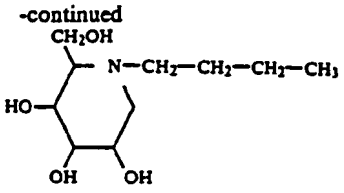
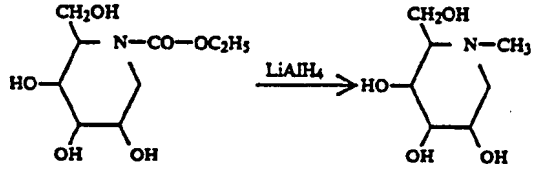
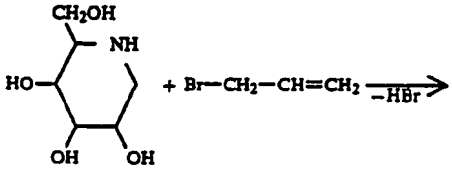
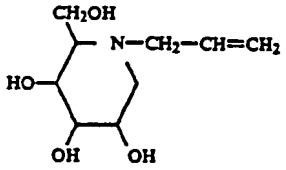


Urethanes of the general formula VIII, optionally in the form of derivatives provided with hydroxyl-protective groups, may be reduced to N-methyl-1-desoxynorjirimycin with $LiAlH_4$:



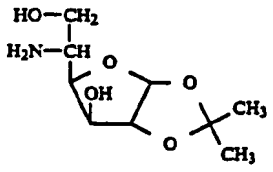
For the reaction of 1-desoxynorjirimycin with an alkylating agent, the reaction with allyl bromide can be indicated by way of example as follows:





Some of the compounds of the formula II used as starting materials are known. This is the case where R_3 is H, $-CH_2OH$ or $-CH_2NH_2$ and R_1 is H. Other compounds of the formula II or IIa are new; however, they can be prepared from compounds which are known from the literature by processes which are in themselves known.

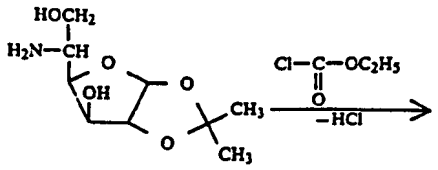
Thus, for example, it is possible to use the compound of the formula X, which is known from the literature,

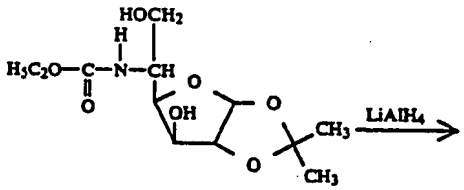


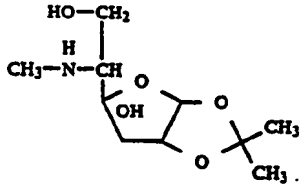
as a starting material and to react this with a carbonyl compound of the formula VI in the presence of a hydrogen donor reducing agent so as to produce a compound of the formula II.

Furthermore, it is possible to react the compound X with reactive acid derivative so as to produce an acid amide or urethane and to reduce this to an amine with an amide-reducing agent.

This can be illustrated by the following example:



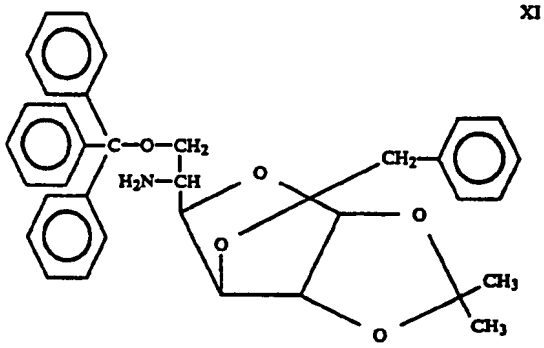




The compound of the formula X can also be reacted with reactive alkylating agents of the following general formula IX as defined hereinbefore

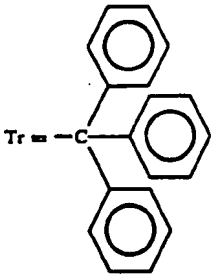
so as to produce a compound of formula II.

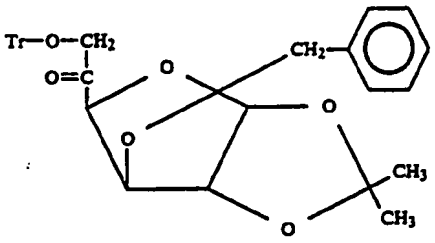
Furthermore, in the above mentioned reactions, instead of the compound X it is also possible to employ known partially protected derivatives of the formula XI



and then to remove the trityl and benzyl protective groups in a known manner, for example with sodium in liquid ammonia. To prepare compounds of the formula II, it is also possible to react the compound of formula XII, which is likewise known from the literature,

XII





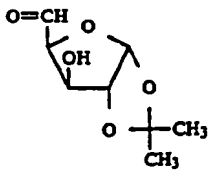
with an amine of the general formula XIII

$$R_1—NH_2 \qquad \text{XIII}$$

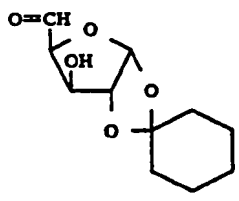
wherein R_1 has the same meaning as defined hereinbefore in formula II, in the presence of a hydrogen donor reducing agent, for example in the presence of $NaBH_3CN$. As a rule, a diastereomer mixture is formed in this reaction. The diastereomer which is not desired may be appropriately separated off at this stage or at a later stage by the customary chromatographic methods or by fractional crystallisation. Finally, the trityl and benzyl protective groups can be split off in a known way, for example with sodium in liquid ammonia.

Moreover, new compounds of the formula II or IIa can also be obtained by reaction of one or more of the degradation products of D-glucose, which are known from the literature, of the formulae XIV to XVI

XIV



XV



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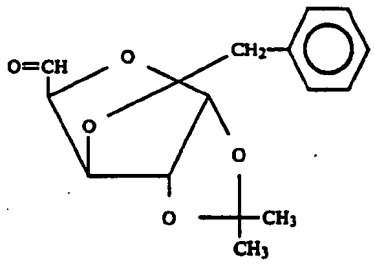
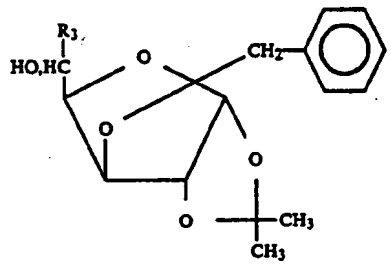
XVI



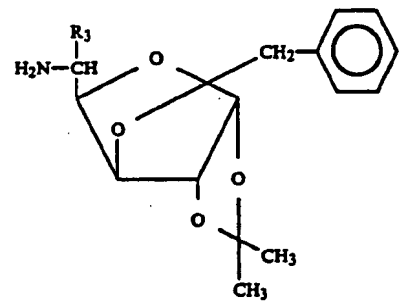
with an appropriate reagent having a carbanion character, such as, for example, alkyl-Li or Grignard compounds or the Li salt of 1,3-dithiane, so as to introduce a group R_3 as defined hereinbefore in formula I, and converting the resulting compound(s) of formula XVII

XVII



in which R_3 has the same meaning as defined hereinbefore in formula I, into the corresponding amine(s) in a manner which is in itself known [S.INOUYE et al., Tetrahedron 23, 2125-2144] via the ketone and the oxime, whereupon, as a rule, a mixture of the gluco compound and ido compound forms, from which the desired gluco compound of formula XVIII

XVIII

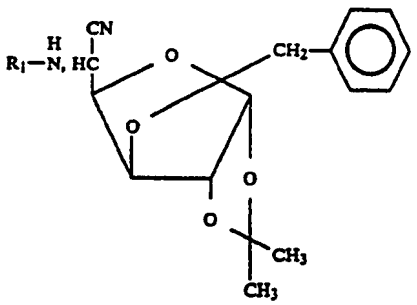


in which R_3 has the same meaning as defined immediately hereinbefore, can be isolated by customary chromatographic methods.

Removal of the benzyl protective group conveniently by catalytic hydrogenation or with Na in liquid NH_3, then gives the corresponding compound(s) of the formula II.

Compounds of the formula XIX (below) can be obtained when an appropriate aldehyde of any of the formulae XIV to XVI is reacted with an appropriate amine and hydrocyanic acid in a manner which is in itself known so as to produce an aminonitrile thereby introducing a group R_1 as defined hereinbefore in formula I.

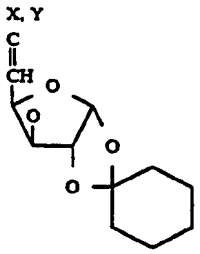
Thus for example a compound of formula XVI is reacted to produce a compound of formula XIX



XIX

wherein R_1 has the same meaning as defined hereinbefore in formula I, and in this case also, as a rule, the desired gluco compound must be separated off from the ido compound by customary chromatographic methods. Further conversion of the nitrile group by hydrogenation or hydrolysis before or after the removal of the benzyl protective group leads to further compounds of the formula II.

The reaction of a compound of formula XIV, XV or XVI with a CH-acid compound, such as, for example, a nitroalkane, alkylnitrile, CH-acid ester or ketone can also lead to compounds of the formula II. In this case, unsaturated compounds, for example compounds of the formula XX, can be obtained:



XX

wherein

X is $-NO_2$, $-CN$ or $-COO$alkyl, and

Y is H, alkyl or aryl,

either directly or by dehydration of the aldol addition product, and these compounds yield compounds of the formula IIa by a Michael addition reaction with an amine, after chromatographic separation of gluco and ido isomers.

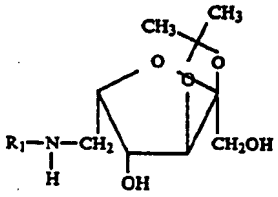
The isopropylidene protective group can be split off from a compound of the formula II in a moderately strongly acid to weakly acid solution, preferably at a pH in the range from 1 to 4, in aqueous solution or in a water-miscible, water-containing organic solvent. Acids which can be used are dilute mineral acids, such as, for example, sulphuric acid, or also organic acids, such as acetic acid. The reaction is preferably carried out under atmospheric pressure and at a temperature from room temperature to the boiling point of the solvent.

In order to work up the reaction mixture, the acid is desirably neutralized and separated off as a salt or with the aid of a basic ion exchanger. The isolation of the compounds of formula I in which R_2 is OH may then appropriately be effected by careful removal of the solvent, for example by lyophilization.

A preferred embodiment of the process of splitting off of the isopropylidene protective group from a compound of the formula II comprises saturation of the aqueous or water-containing alcoholic solution of the compound of the formula II with SO_2 and storing the saturated solution at a temperature of from 20° to 50° C. for several days. The compounds of the formula I can then be obtained as bisulphite adducts (R_2=—SO_3H), which in most cases readily crystallize, from which the compounds of the formula I can be liberated with the aid of, for example, aqueous $Ba(OH)_2$.

A compound of the formula I in which R_2 is OH can be reduced to a compound of the formula I in which R_2 is H by using an alkali metal borohydride, alkali metal cyanoborohydride or dialkylaminoborane. It is preferable to use sodium borohydride in aqueous solution or in a water-miscible water-containing organic solvent, such as, for example, dioxane, at room temperature or optionally elevated temperature. However, the reduction is very particularly preferably carried out catalytically with Pt or Pd as the catalyst or in the presence of Raney Ni. In this procedure, it is preferably carried out in an aqueous solution at room temperature.

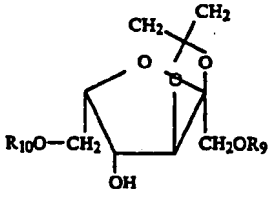
Compounds of the formula I are further obtained from compounds of the formula



(XXI)

by hydrolysis with strong mineral acid of pH<1 at −20° to +20° C. and subsequent hydrogenation at pH 4 to 6 with for instance H_2/Ransey-Nickel, $H_2/P+O_2$ or sodium borohydride.

The compound of the formula XXi can be prepared from compounds of the formula



wherein R_9 is hydrogen or acetyl and R_{10} is mesyl or tosyl, by reaction with amines of the formula

$R_1—NH_2$

at 20° to 150° C. in a polar solvent, e.g. an alkohol, dimethylsulfoxide or in an excess of the amine.

The starting material of the general formula V, in which R_3 is $—CH_2OH$, is known and can be obtained either by catalytic hydrogenation of nojirimycin, which is obtainable by fermentation [S.INOUYE et al., Tetrahedron 23, 2125–2144 (1968)], or by extraction from mulberry tree bark (see DT-OS (German Published Specification) No. 2,656,602), or entirely synthetically. 1-Desoxynojirimycin can also be conveniently prepared by a new advantageous process comprising cultivating an organism of the Bacillaceae family in a customary

fermentation vessel in a customary nutrient medium at a temperature of from about 15° to about 80° C. for from about 1 to about 8 days, with aeration, centrifuging off the cells and isolating the desoxy compound from the culture broth or the cell extracts by a customary purification process (see German Patent Application P No. 26 58 563.7).

The carbonyl compounds of the formula VI are either known or can be prepared by standard processes. Typical examples which may be mentioned and preferably contain up to 8 carbon atoms, are: straight-chain or branched alkylaldehydes, such as formaldehyde, acetaldehyde, n-propanol, n-butanal, 2-methylpropanol, n-pentanal, 2-methylbutanal, 3-methylbutanal, 2,2-dimethyl-propanal, n-hexanal, 2-ethylbutanal, n-heptanal and n-octanal; alkenylaldehydes, such as propenal, 2-methylpropenal, 2-butenal, 2-methyl-2-butenal and 2-ethyl-2-hexenal; cyclic (particularly cycloakyl aldehydes) aldehydes, such as cyclopropanecarbaldehyde, cyclopentanecarbaldehyde, cyclopentaneacetaldehyde and cyclohexanecarbaldehyde; benzaldehyde, o-, m- and p-toluenecarbaldehyde and phenylacetaldehyde; straight-chain and branched alkylaldehydes which are substituted by hydroxyl, such as 5-hydroxypentanal, 2-hydroxy-3-methylbutanal, 2-hydroxy-2-methylpropanal, 4-hydroxybutanal, 2-hydroxypropanal and 8-hydroxyoctanal; straightchain and branched alkylaldehydes which are substituted by amino, such as 5-aminopentanal, 2-aminopropanal, 3-aminopropanal, 4-aminobutanal, 2-amino-3-methylbutanal, 8-amino-octanal and mono-N-alkyl derivatives thereof; and straight-chain and branched alkylaldehydes which are disubstituted by amino and hydroxyl, such as 2-hydroxy-5-aminopentanal, 3-hydroxy-3-methyl-4-aminobutanal, 2-hydroxy-4-aminobutanal, 2-hydroxy-3-aminopropanal, 2-hydroxy-2-methyl-3-aminopropanal, 2-amino-3-hydroxyoctanal and mono-N-alkyl derivatives, particularly C_1–C_8-N-alkyl, thereof.

Furthermore: methoxy-acetaldehyde, ethoxy-acetaldehyde, n-propoxy-acetaldehyde, i-propoxy-acetaldehyde, n-butoxy-acetaldehyde, i-butoxy-acetaldehyde, tert.-butoxyacetaldehyde, cyclopropylmethoxy-acetaldehyde, cyclopropoxyacetaldehyde, 2-methoxy-ethoxy-acetaldehyde, 2-ethoxy-ethoxy-acetaldehyde, 2-methoxy(1-methyl-ethoxy)-acetaldehyde, 2-ethoxy(1-methyl-ethoxy)-acetaldehyde, phenoxy-acetaldehyde, 2-methoxy-2-methyl-acetaldehyde, 2-ethoxy-2-methyl-acetaldehyde, 2-n-propoxy-2-methyl-acetaldehyde, 2-(i-propoxy)-2-methyl-acetaldehyde, 2-(n-butoxy)-2-methyl-acetaldehyde, 2-(i-butoxy)-2-methyl-acetaldehyde, 2-(tert.-butoxy)-2-methyl-acetaldehyde, 2-cyclopropylmethoxy-2-methyl-acetaldehyde, 2-cyclopropoxy-2-methyl-acetaldehyde, 2-methoxy-ethoxy-α-methyl-acetaldehyde, 2-ethoxy-ethoxy-α-methyl-acetaldehyde, 2-methoxy-(1-methyl-ethoxy)-α-methyl-acetaldehyde, 2-methoxy-2,2-dimethylacetaldehyde, 2-ethoxy-2,2-dimethylacetaldehyde, 2-cyclopropylmethoxy-acetaldehyde, 2-ω-butoxy-2,2-dimethyl-acetaldehyde, methylthio-acetaldehyde, ethylthio-acetaldehyde, n-propylthio-acetaldehyde, i-propylthioacetaldehyde, cyclopropyl-methylthioacetaldehyde, 3-methoxy-propanal, 3-ethoxy-propanal, 3-n- and 3-i-propoxypropanal, 3-n-, 3-i- and 3-tert.-butoxy-propanal, 3-cyclopropoxy-propanal, 3-cyclopropylmethoxy-propanal, 3-methoxy-3-methyl-propanal, 3-ethoxy-3-methyl-propanal, 3-n- and 3-i-propoxy-3-methyl-propanal, 3-n-, 3-i- and 3-tert.-butoxy-3-methyl-propanal, 2-,3- and 4-methoxy-butanal, 2-,3- and 4-ethoxy-butanal, 2-methylthio-propanal, 2-ethylthio-propanal, 3-methyl-thio-propanal, 3-ethylthio-propanal, 2-methylthio-butanal, 3-methylthio-butanal, 4-methylthiobutanal, furfurol, tetrahydrofurfurol, thiophene, 5-bromothiophene, 5-methylfurfurol and pyrane-carbaldehyde.

In addition, examples of ketones which may be mentioned are particularly those which are hydrocarbon except for the oxo groups but also those containing additional substituents, such as C_1–C_4-alkoxy and nitro: acetone, methyl ethyl ketone, methyl n-propyl ketone, diethyl ketone, methyl butyl ketone, cyclopentanone, di-n-propyl ketone, cyclohexanone, 3-methylcyclohexanone, 4-methylcyclohexanone, acetophenone, propiophenone, butyrophenone, phenylacetone, p-methoxyacetophenone and m-nitroacetophenone.

Formic acid, for example, can be used as the hydrogen donor reducing agent (Leuckart-Wallach reaction). The formic acid is generally used in a large excess. If formaldehyde is used as the carbonyl reaction component, the reaction can be carried out in aqueous solution, and if ketones and less reactive aldehydes are used, it can be carried out in anhydrous formic acid. The reaction temperature is generally from 100° to 200° C., and if appropriate the reaction should be carried out in an autoclave.

Catalytically activated hydrogen can also be used as the hydrogen donor reducing agent. A possible catalyst is most preferably, Raney nickel, but noble metal catalysts, particularly those of Group VIII of the Periodic System, can also be used. In general, the reaction is carried out under a pressure of from 80 to 150 atmospheres of H_2 pressure and at a temperature of from 70° to 150° C. Preferred solvents are protic, polar solvents, especially alcohols, more particularly alkanols, such as methanol, ethanol, propanol and isopropanol.

Alkali metal cyanoborohydrides, dialkylaminoboranes and alkali metal borohydrides can also be used as hydrogen donor reducing agents. In this process variant, the use of sodium cyanoborohydride is particularly preferred.

In general, the reaction is carried out at room temperature. However, it can also be advantageous to heat the mixture to the reflux temperature of the reaction medium.

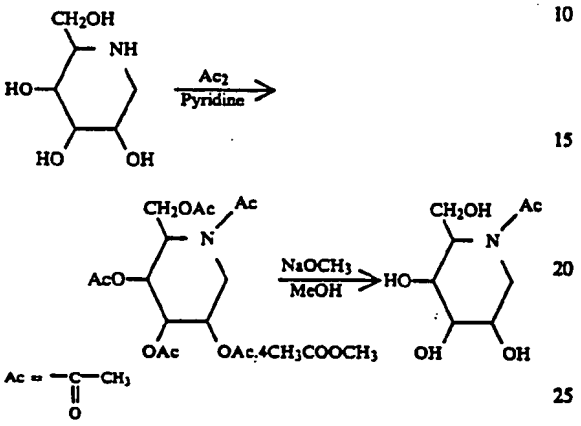
The process is usually carried out in an inert solvent. Although anhydrous aprotic solvents can be employed (for example tetrahydrofurane, when the reducing agent is morpholinoborane), a protic solvent is usually used. A suitable protic solvent is, in particular, a lower alkanol. However, water or an aqueous lower alkanol (for example aqueous methanol or ethanol) or other aqueous solvent system, such as, for example, aqueous dimethylformamide, aqueous hexamethylphosphoric acid triamide, aqueous tetrahydrofurane or aqueous ethylene glycol dimethyl ether, may also be used.

The process is usually carried out in a pH range of from 1 to 11, though a pH range of from 4 to 7 is preferred.

The acid amides of the general formula VII and urethanes of the general formula VIII are known in some cases, or they can be obtained by known processes from a compound of formula V and a reactive acid derivative, which can also be formed in situ from the corresponding free acid.

In this procedure, the reaction can be carried out in a manner such that only the amino group of the compound of formula V reacts with the acid derivative, for

example by using excess acid anhydride in an aqueous or alcoholic (e.g. C_1-C_3-alkanolic) solution, or such that the peracylated compounds first form and are then converted into the N-acylated compounds by reaction with alcoholic ammonia or by trans-esterification catalyzed by alkali metal alcoholate. The latter process can be illustrated by way of example by the following reaction scheme:

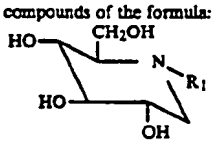


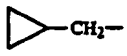
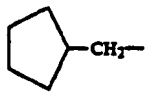
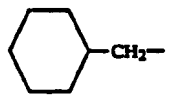
An acid amide of the general formula II can be reduced to the corresponding amine of the formula I (R=H) with a complex metal hydride or with a boron hydride compound. It is preferable to use $NaBH_4$ in pyridine or a sodium acyloxyborohydride, particularly sodium trifluoroacetoxyborohydride. In general, the reducing ahgent is employed in excess. Sodium trifluoroacetoxyborohydride can be produced in situ from sodium borohydride and trifluoroacetic acid. Possible solvents are, in addition to pyridine, polar aprotic solvents, such as dioxane, tetrahydrofurane or diglyme. The reaction is preferably carried out at the boiling point of the solvent used. $LiAlH_4$ can also optionally be used for the reduction, preferably when the hydroxyl groups are first protected in the customary way.

The reactive alkylating agents of the general formula IX are known or can be prepared by customary processes. The reaction with a compound of formula V can be carried out in an inert organic solvent, generally at from room temperature up to the boiling point of the reaction medium, with or without the addition of an acid-binding agent.

Specific new active compounds according to the invention which may be mentioned are:

compounds of the formula:



R_1
CH_3
CH_3CH_2-
$CH_3CH_2CH_2-$
CH_3CHCH_3 (|)
$CH_3CH_2CH_2CH_2-$
$CH_3-CH(CH_3)-CH_2-CH_3$
H_3C, $CH-CH_2-$, H_3C
H_3C, H_3C-C-, H_3C
$CH_3(CH_2)_3-CH_2-$
H_3C, $CH-CH_2-CH_2-$, H_3C
$CH_3-CH(CH_3)-CH_2CH_3$
$CH_3CH_2-CH(CH_3)-CH_2CH_3$
$CH_3CH(CH_3)CH_2CH_2-$
$CH_3(CH_2)_4-CH_2-$
$CH_3(CH_2)_5-CH_2-$
$CH_3CH(CH_3)CH_2CH_2CH_2-$
$CH_3CH(CH_3)-(CH_2)_3-CH_2-$
$CH_3(CH_2)_6-CH_2-$
$CH_3CH(CH_3)-(CH_2)_4-CH_2-$
$CH_3-(CH_2)_8-CH_2-$
$CH_3-(CH_2)_{10}-CH_2-$
$CH_3-(CH_2)_{12}-CH_2-$
$CH_3-(CH_2)_{14}-CH_2-$
$CH_3-(CH_2)_{16}-CH_2-$




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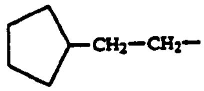


HO—CH_2—CH_2—

H_3C—CH(OH)—CH_2—

HOH_2C—CH_2—CH_2—

HOH_2C—CH_2—CH_2—CH_2—

HOH_2C—$(CH_2)_3$—CH_2—

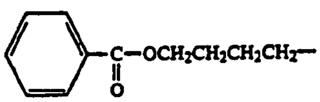
CH_3—CH(CH_3)—CH(OH)—CH_2—

HO—CH_2—CH(OH)—CH_2—

CH_3OCH_2—CH_2—

$C_3H_7OCH_2$—CH_2—

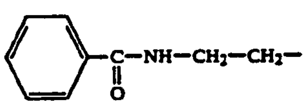
CH_3COOCH_2—CH_2—



H_2N—CH_2—CH_2—

$(H_3C)_2$N—CH_2—CH_2—

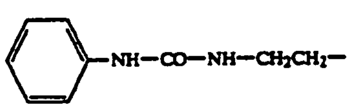
CH_3CONH—CH_2—CH_2—



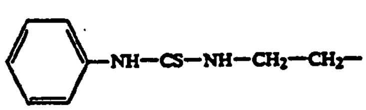
$C_2H_5OC(=O)NH$—CH_2—CH_2—

CH_3CO—N(CH_3)—CH_2—CH_2—

CH_3NH—CO—NH—CH_2CH_2—



CH_3NH—CS—NH—CH_2CH_2—



H_2N—$CH_2CH_2CH_2$—

$CH_3CONHCH_2CH_2CH_2$—

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$CH_3NHCONHCH_2CH_2CH_2$—

H_2N—$CH_2CH_2CH_2CH_2$—

H_2C=CH—CH_2—

H_3C—HC=CH—CH_2—

H_2C=CH—CH_2—CH_2—

H_2C=CH—CH_2—CH_2—CH_2—CH_2—

H_2C=CH—$(CH_2)_7$—CH_2—

HOOC—CH_2—

HOOC—CH_2—CH_2—

H_5C_2OOC—CH_2—CH_2—

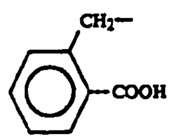
H_2N—C(=O)—CH_2—

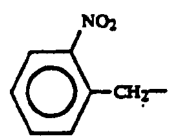
C_2H_5HN—C(=O)—CH_2

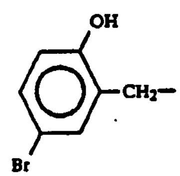
C_4H_9—HN—C(=O)—CH_2

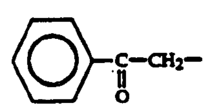
HO_3S—$CH_2CH_2CH_2$—

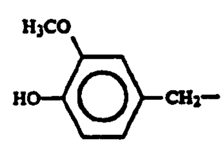
H_2NO_2S—$CH_2CH_2CH_2$—











H—C≡C—CH_2—

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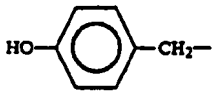

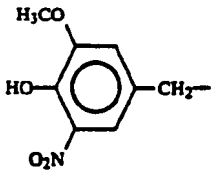

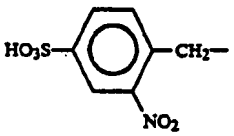

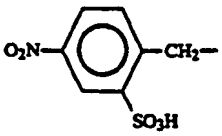

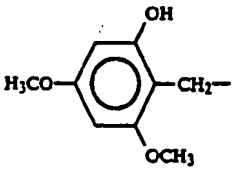

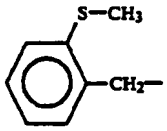

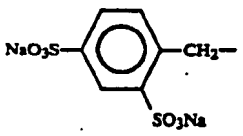

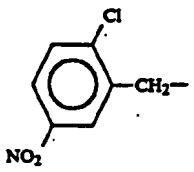

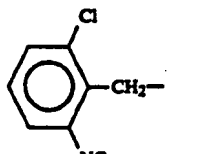

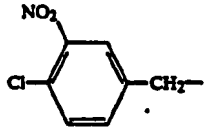

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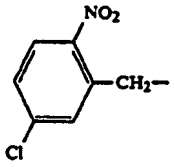

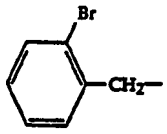

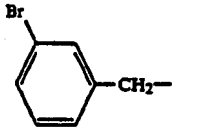

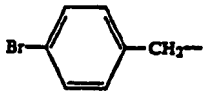

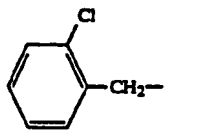

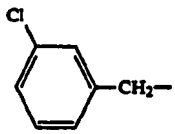

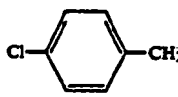

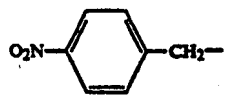

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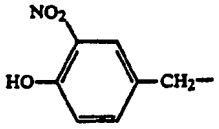

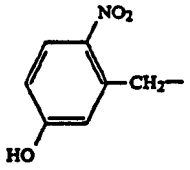

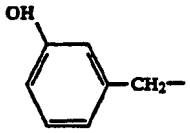

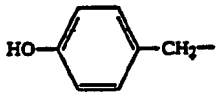

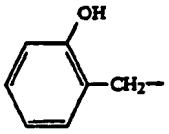

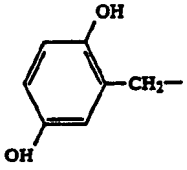

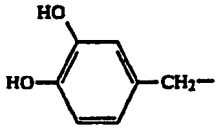

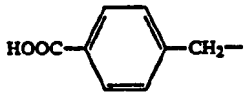

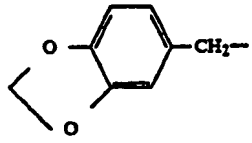

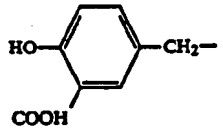

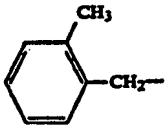

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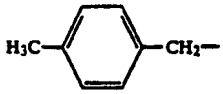

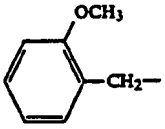

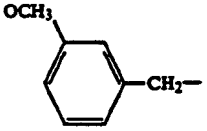

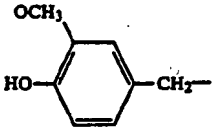

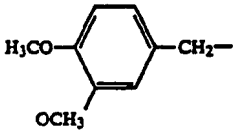

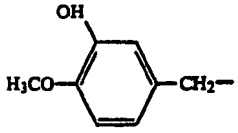

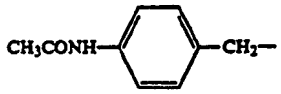

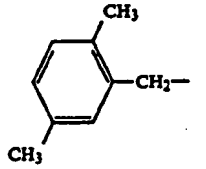

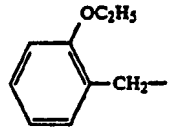

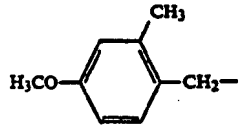

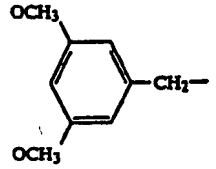

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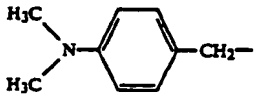

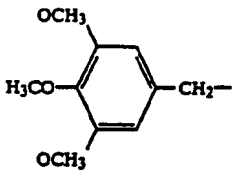

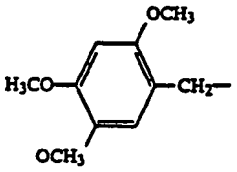

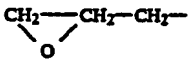

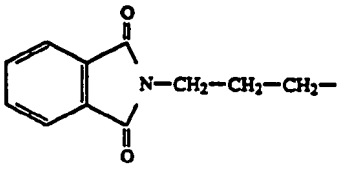

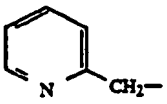

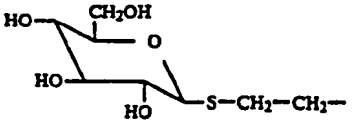

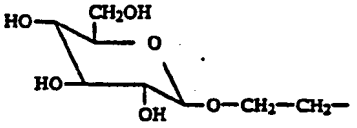

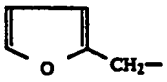

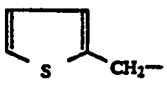

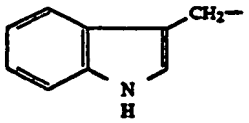

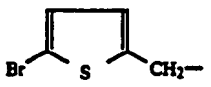

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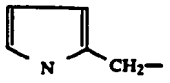
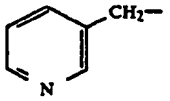
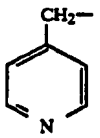
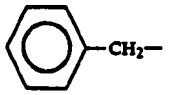
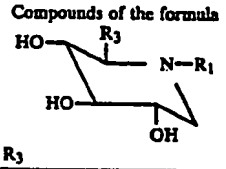


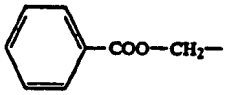
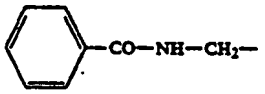
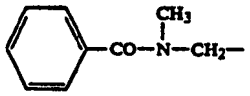




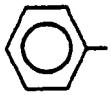
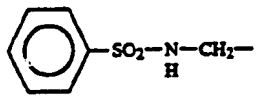
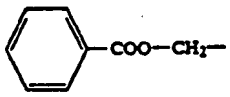
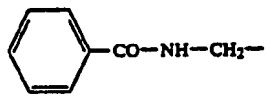
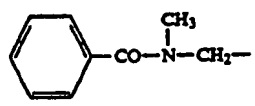
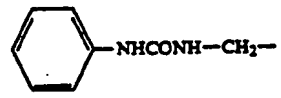


Compounds of the formula

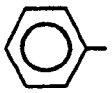
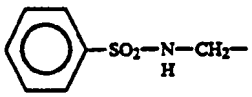


R_1	R_3
H—	CH_3—
H—	CH_3CH_2—
H—	$CH_3CH_2CH_2$—
H—	$CH(CH_2)_6$—CH_2—
H—	H_3C—O—CH_2—
H—	H_5C_2—O—CH_2—
H—	H_3C—COO—CH_2—
H—	
H—	H_2N—CH_2—
H—	CH_3CO—NH—CH_2—
H—	
H—	
H—	$CH_3NHCONH$—CH_2—
H—	
H—	

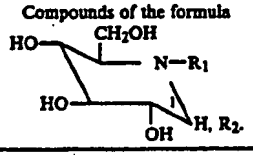
-continued

H—	$C_2H_5OCONH-CH_2-$
H—	$HO-CH_2-CH_2-$
H—	
H—	—COOH
H—	$-CONH_2$
H—	$H_3C-SO_2-N(H)-CH_2-$
H—	$H_3C-H_2C-SO_2-N(H)-CH_2-$
H—	
CH_3—	CH_3-
CH_3—	CH_3CH_2-
CH_3—	$CH_3CH_2CH_2-$
CH_3—	$CH_3(CH_2)_6-CH_2-$
CH_3—	$H_3C-O-CH_2-$
CH_3—	$H_5C_2-O-CH_2-$
CH_3—	$H_3C-COO-CH_2-$
CH_3—	
CH_3—	H_2N-CH_2-
CH_3—	$CH_3CO-NH-CH_2-$
CH_3—	
CH_3—	
CH_3—	$CH_3NHCONH-CH_2-$
CH_3—	
CH_3—	$CH_3-CH_2-N(H)-C(=S)-NH-CH_2-$
CH_3—	$C_2H_5OCONH-CH_2-$
CH_3—	$HO-CH_2-CH_2-$

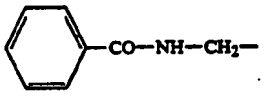
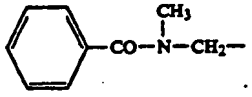
-continued

CH_3—	
CH_3—	—COOH
CH_3—	$-CONH_2$
CH_3—	$H_3C-SO_2-N(H)-CH_2-$
CH_3—	$H_3C-H_2C-H_2C-SO_2-N(H)-CH_2-$
CH_3—	

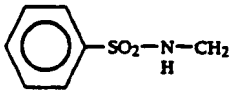
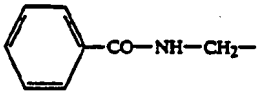
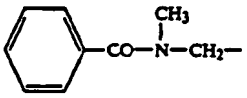
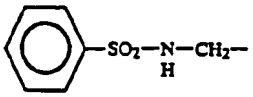
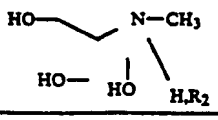
Compounds of the formula



With respect to the configuration at the C-1 atom, the examples listed below include both the α-form and the β-form

R_1	R_2
H—	H_2N-CH_2-
H—	$CH_3CO-NH-CH_2-$
H—	
H—	
H—	$CH_3NHCONH-CH_2-$
H—	
H—	$CH_3-CH_2-N(H)-C(=S)-NH-CH_2-$
H—	$C_2H_5OCONH-CH_2-$
H—	—COOH
H—	$-COOC_2H_5-$
H—	$-CONH_2$
H—	$H_3C-SO_2-N(H)-CH_2$
H	$H_3C-H_2C-H_2C-SO_2-N(H)-CH_2-$

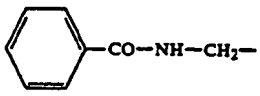
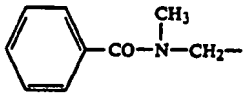
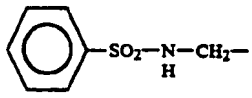
-continued

R_1	R_2
H—	
H—	$HO-CH_2-$
H—	$H_5C_2-COO-CH_2-$
CH_3-	H_2N-CH_2-
CH_3-	$CH_3CO-NHCH_2-$
CH_3-	
CH_3-	
CH_3-	$CH_3NHCONH-CH_2-$
CH_3-	
CH_3-	$CH_3-CH_2-N(H)-C(=S)-NH-CH_2-$
CH_3-	$C_2H_5OCONH-CH_2-$
CH_3-	$-COOH$
CH_3-	$-COOC_2H_5$
CH_3-	$-CONH_2$
CH_3-	$H_3C-SO_2-N(H)-CH_2-$
CH_3-	$H_3C-H_2C-H_2C-SO_2-N(H)-CH_2-$
CH_3-	
CH_3-	$HO-CH_2-$
CH_3-	$H_5C_2-COO-CH_2-$
CH_3-	$-OH$
CH_3-	$-SO_3H$
CH_3-	$-CN$
CH_3-	$-OCH_3$
CH_3-	$-O-CH_2-CH_2-CH_2-CH_3$
CH_3-	$-SH$
CH_3-	$-S-CH_2-CH_3$
CH_3-	$-NH_2$
CH_3-	$-NH-CH_3$
Compounds of the formula	

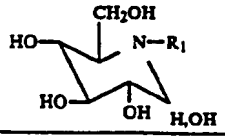
With respect to the configuration at the C-2 atom, the examples listed below include both the α-form and the β-form

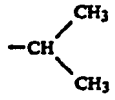
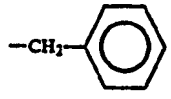
R_2
H_2N-CH_2-
$CH_3CO-NH-CH_2-$

-continued

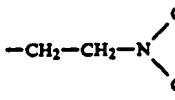
R_1	R_2
	
	
	$CH_3NHCONH-CH_2-$
	
	$CH_3-CH_2-N(H)-C(=S)-NH-CH_2-$
	$C_2H_5OCONH-CH_2-$
	$-COOH$
	$-COOC_2H_5$
	$-CONH_2$
	$H_3C-SO_2-N(H)-CH_2-$
	$H_3C-H_2C-H_2C-SO_2-N(H)-CH_2-$
	
	$HO-CH_2-$
	$H_5C_2-C(=O)-O-CH_2-$

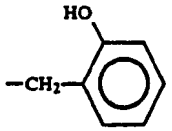
R_2	R_2
$-OH$	$-O-CH_2-CH_2-CH_2-CH_3$
$-CN$	$-SH$
$-SO_3H$	$-S-CH_2-CH_3$
$-OCH_3$	$-NH_2$
	$-NH-CH_3$

Compounds of the formula 

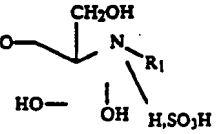
R_1
$-CH_2-CH_3$
$-CH_2-CH_2-CH_2-CH_3-$
$-CH_2-(CH_2)_{16}-CH_3-$


$-CH_2-CH=CH_2-$
$-CH_2-CH_2-OCH_3-$

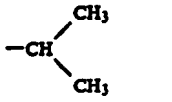
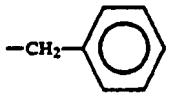
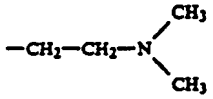
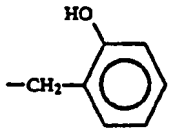
-continued



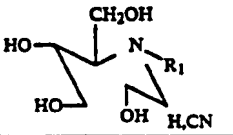


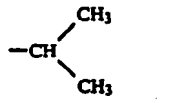
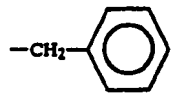
Compounds of the formula



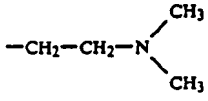
R_1
$-CH_2-CH_3$
$-CH_2-CH_2-CH_2-CH_3$
$-CH_2-(CH_2)_{16}-CH_3$


$-CH_2-CH=CH_2$
$-CH_2-CH_2-OCH_3$



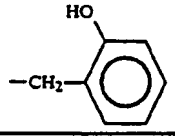
Compounds of the formula



R_1
$-CH_2-CH_3$
$-CH_2-CH_2-CH_2-CH_3$
$-CH_2-(CH_2)_{16}-CH_3$


$-CH_2-CH=CH_2$
$-CH_2-CH_2-OCH_3$

-continued





The inhibitors according to the invention are suitable for use as therapeutic agents for the following indications: prediabetes, gastritis, constipation, infections of the gastro intestinal tract, meteorismus, flatulence, caries, atherosclerosis, hypertension and in particular obesity, diabetes and hyperlipoproteinaemia. To broaden the activity spectrum, it is possible to combine inhibitors for glycoside-hydrolases which complement one another in their action, the combinations being either combinations of two or more compounds according to the invention with one another or combinations of the compounds according to the invention with inhibitors which are already known. Thus, for example, it can be appropriate to combine saccharase inhibitor compounds according to the invention with amylase inhibitors which are already known.

In some cases, combinations of the compounds according to the invention with known oral antidiabetic agents (β-cytotropic sulphonylurea derivatives and/or biguanides having an action on the blood sugar) and with blood lipid-lowering active compounds, such as, for example, clofibrate, nicotinic acid, cholestyramine and others, are advantageous.

The compounds can be administered without dilution, for example as a powder or in a gelatine casing, or in combination with an excipient in a pharmaceutical composition.

The present invention provides a pharmaceutical composition containing as active ingredient a compound of the invention in admixture with a solid or liquefied gaseous diluent, or in admixture with a liquid diluent other than a solvent of a molecular weight less than 200 (preferably less than 350) except in the presence of a surface active agent.

The invention further provides a pharmaceutical composition containing as active ingredient a compound of the invention in the form of a sterile and/or physiologically isotonic aqueous solution.

The invention also provides a medicament in dosage unit form comprising a compound of the invention.

The invention also provides a medicament in the form of tablets (including lozenges and granules), dragees, capsules, pills, ampoules or suppositories comprising a compound of the invention.

"Medicament" as used in this specification means physically discrete coherent portions suitable for medical administration. "Medicament in dosage unit form" as used in this specification means physically discrete coherent units suitable for medical administration each containing a daily dose or a multiple (up to four times) or sub-multiple (down to a fortieth) of a daily dose of the compound of the invention in association with a carrier and/or enclosed within an envelope. Whether the medicament contains a daily dose, or for example, a half, a third, or a quarter of a daily dose will depend on

whether the medicament is to be administered once or, for example, twice, three times or four times a day respectively.

The pharmaceutical compositions according to the invention may, for example, take the form of suspensions, solutions and emulsions of the active ingredient in aqueous or non-aqueous diluents, syrups, granulates or powders.

The diluents to be used in pharmaceutical compositions (e.g. granulates) adapted to be formed into tablets, dragees, capsules and pills include the following: (a) fillers and extenders, e.g. starch, sugars, mannitol, and silicic acid; (b) binding agents, e.g. carboxymethyl cellulose and other cellulose derivatives, alginates, gelatine and polyvinyl pyrrolidone; (c) moisturizing agents, e.g. glycerol; (d) disintegrating agents, e.g. agar-agar, calcium carbonate and sodium bicarbonate; (e) agents for retarding dissolution e.g. paraffin; (f) resorption accelerators, e.g. quaternary ammonium compounds; (g) surface active agents, e.g. cetyl alcohol, glycerol monostearate; (h) adsorptive carriers, e.g. kaolin and bentonite; (i) lubricants, e.g. talc, calcium and magnesium stearate and solid polyethylene glycols.

The tablets, dragees, capsules and pills formed from the pharmaceutical compositions of the invention can have the customary coatings, envelopes and protective matrices, which may contain opacifiers. They can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes and protective matrices may be made, for example, of polymeric substances or waxes.

The ingredient can also be made up in microencapsulated form together with one or several of the above mentioned diluents.

The diluents to be used in pharmaceutical compositions adapted to be formed into suppositories can, for example, be the usual water-soluble or water-insoluble diluents, such as polyethylene glycols and fats (e.g. cocoa oil and high esters [e.g. C_{14}-alcohol with C_{16}-fatty acid]) or mixtures of these diluents.

The pharmaceutical compositions which are solutions and emulsions can, for example, contain the customary diluents (with, of course, the above mentioned exclusion of solvents having a molecular weight below 200 except in the presence of a surface-active agent), such as solvents, dissolving agents and emulsifiers; specific examples of such diluents are water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils [for example ground nut oil], glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitol or mixtures thereof.

For parenteral administration, solutions and emulsions should be sterile, and, if appropriate, blood-isotonic.

The pharmaceutical compositions which are suspensions can contain the usual diluents, such as liquid diluents, e.g. water, ethyl alcohol, propylene glycol, surface-active agents (e.g. ethoxylated isostearyl alcohols, polyoxyethylene sorbite and sorbitane esters), microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragacanth or mixtures thereof.

All the pharmaceutical compositions according to the invention can also contain colouring agents and preservatives as well as perfumes and flavoring additions (e.g. peppermint oil and eucalyptus oil) and sweetening agents (e.g. saccharin).

The pharmaceutical compositions according to the invention generally contain from 0.1 to 99.5, usually from 0.5 to 95% of the active ingredient by weight of the total composition.

In addition to a compound of the invention, the pharmaceutical compositions and medicaments according to the invention can also contain other pharmaceutically active compounds. They may also contain a plurality of compounds of the invention.

Any diluent in the medicaments of the present invention may be any of those mentioned above in relation to the pharmaceutical compositions of the present invention. Such medicaments may include solvents of molecular weight less than 200 as sole diluent.

The discrete coherent portions constituting the medicament according to the invention will generally be adapted, by virtue of their shape or packaging, for medical administration and may be, for example, any of the following: tablets, (including lozenges and granulates), pills, dragees, capsules, suppositories and ampoules. Some of these forms may be made up for delayed release of the active ingredient. Some, such as capsules, include a protective envelope which renders the portions of the medicament physically discrete and coherent.

The preferred daily dose for administration of the medicaments of the invention is from 500 to 5×10^6 SIU (as defined hereinbelow) or from 1 to 3500 mg, most preferably from 10 to 500 mg active ingredient.

The production of the above mentioned pharmaceutical compositions and medicaments is carried out by any method known in the art, for example, by mixing the active ingredient(s) with the diluent(s) to form a pharmaceutical composition (e.g. a granulate) and then forming the composition into the medicament (e.g. tablets).

This invention further provides a method of combating (including prevention, relief and cure of) the above mentioned diseases in warm-blooded animals, which comprises administering to the animals a compound of the invention alone or in admixture with a diluent or in the form of a medicament according to the invention.

It is envisaged that these active compounds will be administered perorally, parenterally (for example intramuscularly, intraperitoneally, subcutaneously or intravenously), rectally or locally, preferably orally. Preferred pharmaceutical compositions and medicaments are therefore those adapted for oral administration, such as tablets, capsules, powders, dragees, granules, suspensions and solutions. Administration in the method of the invention is preferably orally.

In general it has proved advantageous to administer amounts of from 10 to 1×10^4 SIU (as defined hereinbelow) or amounts of from 0.01 mg to 100 mg, preferably from 0,1 to 10 mg, per kg of body weight per day to achieve effective results. Nevertheless, it can at times be necessary to deviate from those dosage rates, and in particular to do so as a function of the nature and body weight of the human or animal subject to be treated, the individual reaction of this subject to the treatment, the type of formulation in which the active ingredient is administered and the mode in which the administration is carried out, and the point in the progress of the disease or interval at which it is to be administered. Thus it may in some case suffice to use less than the above mentioned minimum dosage rate, whilst other cases the

upper limit mentioned must be exceeded to achieve the desired results. Where larger amounts are administered it can be advisable to divide these into several individual administrations over the course of the day.

In addition to the above mentioned pharmaceutical compositions, foodstuffs containing these active compounds can also be prepared; for example sugar, bread, potato products, fruit juice, beer, chocolate and other confectionery, and preserves, such as, for example, jam, a therapeutically active amount of at least one of the inhibitors according to the invention having been added to these products.

The food products produced using the active compounds according to the invention are suitable for use both in the diet of patients suffering from metabolic disorders and for the nutrition of healthy persons in the sense of a method of nutrition for the prophylaxis of metabolic disorders.

Furthermore, the inhibitors according to the invention have the property, in animals, of influencing to a high degree the ratio of the proportion of undesired fat to the proportion of desired meat of low fat content (lean meat) in favour of the lean meat. This is of particular importance for the rearing and keeping of agricultural stock animals, for example in the fattening of pigs, but is also of considerable importance for the rearing and keeping of other stock animals and pets. Furthermore, the use of the inhibitors can lead to a considerable rationalisation of the feeding of the animals, both in respect of time, quantity and quality. Since they cause a certain delay in digestion, the residence time of the nutrients in the digestive tract is extended, whereby ad libitum feeding associated with less expense is made possible. Furthermore, in many cases there is a considerable saving of valuable protein feed when the inhibitors according to the invention are used.

The active compounds can thus be used in virtually all spheres of animal nutrition as agents for reducing the formation of fatty layers and for the conservation of feed protein.

The activity of the active compounds is essentially independent of the nature and the sex of the animals. The active compounds prove particularly valuable in species of animals which tend generally to deposit relatively large amounts of fat, or tend to do so during certain stages of their life.

The following stock animals and pets may be mentioned as examples of animals for which the inhibitors for reducing the formation of fatty layers and/or for conserving feed protein can be employed: warm-blooded animals, such as cattle, pigs, horses, sheep, goats, cats, dogs, rabbits, fur-bearing animals, for example mink and chinchillas, and other pets, for example guineapigs and hamsters, laboratory animals and zoo animals, for example rats, mice, monkeys and the like, poultry, for example broilers, chickens, geese, ducks, turkeys and pigeons, parrots and canaries, and cold-blooded animals, such as fish, for example carp, and reptiles, for example snakes.

Because of the advantageous properties of the active compounds of the invention, the amount of active compound administered to the animals in order to achieve the desired effect can be varied within broad limits. It is preferably from 0,1 to 1000 mg most preferably from 1.0 to 100 mg/kg of feed per day. The period over which the active compound is administered can be from a few hours or days to several years. The appropriate amount of active compound and the appropriate period over which it is administered are closely connected with the object of feeding. In particular, they depend on the nature, the age, the sex and the state of health and the method of keeping the animals and can be easily determined by any expert.

The active compounds according to the invention may be administered to the animal by customary methods. The nature of the administration route depends, in particular, on the nature, the behaviour and the general condition of the animals. Thus it is possible to carry out the administration orally once or several times daily, at regular or irregular intervals. In most cases, oral administration, in particular in synchromism with the food and/or drink intake of the animals, is to be preferred for reasons of expediency.

The active compounds of the invention may be administered as pure substances or in a formulated form, the expression "formulated form" including both a premix for admixture with the animal feed or drinking water, that is to say mixed with a non-toxic carrier of any desired nature, and also as part of a total ration in the form of a supplementary feed and as a constituent of the mixture of a mixed feed by itself. Administration of suitable formulations by means of the animal drinking water is also included.

The active compounds according to the invention, optionally in the formulated form, can also be administered, in a suitable form, together with other nutrients and active compounds, for example mineral salts, trace elements, vitamins, proteins, energy carriers (for example starch, sugar or fats), dyestuffs and/or flavouring substances or other feedstuff additives, such as, for example, growth promoters. The active compounds of the invention can be administered to the animals before, during or after their food intake.

Oral administration together with the feed and/or drinking water is advisable, the active compounds being added to the total amount or only to certain parts of the feed and/or drinking water, depending on the requirement.

The active compounds of the invention can be added to the feed and/or the drinking water according to customary methods by simple admixture of the pure compound, preferably in a finely divided form, or in a formulated form mixed with edible, non-toxic carriers, and optionally also in the form of a premix or a feed concentrate.

The feed and/or drinking water can, for example, contain the active compounds according to the invention in a concentration of from 0.001 to 5.0‰, most preferably from 0.01 to 2.0‰ (by weight). The optimum level of the concentration of the active compound in the feed and/or drinking water depends, in particular, on the size of the feed and/or drinking water intake of the animals and can be easily determined by any person skilled in the art.

The nature of the feed itself and its composition does not normally influence the utilization of the compounds of the invention. Thus it is possible to use all the current, commercially available or special feed compositions, which preferably contain the customary proportions of energy substances and proteins, including vitamins and mineral substances, necessary for balanced nutrition. The feed can be composed, for example, of vegetable substances, for example shredded oil-cake, shredded cereal and cereal by-products, but also of hay, silage fodder, beets, and other forage plants, of animal substances, for example meat and fish products, bonemeal,

fats and vitamins, for example A, D, E, K and B-complex, as well as special sources of protein, for example yeasts and certain amino-acids, and mineral substances and trace elements, such as, for example, phosphorus and iron, zinc, manganese, copper, cobalt, iodine and the like.

Premixes can preferably contain from 0.1 to 50%, most preferably from 0.5 to 5.0% (by weight) of, for example, N-methyl-1-desoxynorjirimycin, in addition to any desired eedible carrier and/or mineral salt, for example carbonated feed lime, and may be prepared by customary mixing methods.

Mixed feeds preferably contain from 0.001 to 5.0‰, in particular from 0.02 to 2.0‰ (by weight), for example, of N-methyl-1-desoxynorjirimycin, in addition to the customary raw material components of a mixed feed, for example shredded cereal or cereal by-products, shredded oilcake, animal protein, minerals, trace elements and vitamins. They can be prepared by customary mixing methods.

The active compounds of the invention when in premixes and mixed feedstuffs can preferably also be appropriately protected from air, light and/or moisture by suitable agents which cover their surface, for example with nontoxic waxes or gelatine.

The following is an example of a composition of a finished mixed feed, for poultry, containing an active compound according to the invention: 200 g of wheat, 340 g of maize, 360.3 g of coarse soya bean meal, 60 g of beef tallow, 15 g of dicalcium phosphate, 10 g of calcium carbonate, 4 g of iodinated sodium chloride, 7.5 g of a vitamin/mineral mixture and 3.2 g of an active compound premix yielding, after careful mixing, 1 kg of feed.

The vitamin/mineral mixture consists of: 6,000 I.U. of vitamin A, 1,000 I.U. of vitamin D_3, 10 mg of vitamin E, 1 mg of vitamin K_3, 3 mg of riboflavin, 2 mg of pyridoxine, 20 meg of vitamin B_{12}, 5 mg of calcium pantothenate, 30 mg of nicotinic acid, 200 of choline chloride, 200 mg of $MnSO_4 \times H_2O$, 140 mg of $ZnSO_4 \times 7H_2O$, 100 mg of $FeSO_4 \times 7H_2O$ and 20 mg of $CuSO_4 \times 5H_2O$. The active compound premix contains, for example, N-methyl-1-desoxynojirimycin in the desired amount, for example 1,600 mg, and in addition 1 g of DL-methionine and enough soya bean flour to form 3.2 g of premix.

The following is an example of the composition of a mixed feed for pigs, which feed contains an active compound of the formula I: 630 g of shredded cereal feed (composed of 200 g of shredded maize, 150 g of shredded barley, 150 g of shredded oats and 130 g of shredded wheat), 80 g of fishmeal, 60 g of coarse soya bean meal, 58.8 g of tapioca flour, 38 g of brewer's yeast, 50 g of a vitamin/mineral mixture for pigs (constitution for example, as in the chicken feed above), 30 g of linseed cake meal, 30 g of maize gluten feed, 10 g of soya bean oil, 10 g of cane sugar molasses and 2 g of active compound premix (constitution for example, as in the chicken feed above) yield, after careful mixing, 1 kg of feed.

The feed mixtures indicated are intended, preferably, for the rearing and fattening of chickens or pigs respectively; however, they can also be used in identical or similar compositions for the rearing and fattening of other animals.

The compounds of the invention can be used individually or in any desired mixture with one another.

In vitro saccharase inhibition test

The in vitro saccharase inhibition test makes it possible to determine the enzyme-inhibitory activity of a substance by comparison of the activity of the solubilised intestinal disaccharidase complex in the presence and in the absence (so-called 100% value) of the inhibitor (compound under scrutiny). A virtually glucose-free sucrose (glucose < 100 ppm) is used here as the substrate which determines the specificity of the inhibition test; the determination of enzyme activity is based on the spectrophotometric determination of glucose liberated, using glucose dehydrogenase and nicotinamide-adenine dinucleotide as the cofactor.

One saccharase inhibitor unit (SIU) is defined as that inhibitory activity which, in a defined test batch, reduces a given saccharolytic activity by one unit (saccharase unit = SU); the saccharase unit being defined here as that enzyme activity which splits off one μmol of sucrose per minute under given conditions and thus leads to the liberation of one μmol each of glucose, which is determined in the test, and fructose, which is not recorded in the test.

The intestinal disaccharidase complex is obtained from swine small intestine mucosa by tryptic digestion, precipitation from 66% strength ethanol at −20° C., taking up of the precipitate in 100 mM phosphate buffer, pH 7.0, and finally dialysis against the same buffer.

100 μl of a dilution of the intestinal disaccharidase complex in 0.1M maleate buffer, pH 6.25, are added to 10 μl of a sample solution, which is prepared so that the extinction of the test batch is at least 10%, but not more than 25%, below that of the 100% value, and the mixture is pre-incubated at 37° C. for 10 minutes. The dilution of the disaccharidase complex should normally be adjusted to an activity of 0.1 SU/ml.

The saccharolytic reaction is started by adding 100 μl of a 0.4M solution of sucrose ("SERVA 35579") in 0.1M maleate buffer, pH 6.25, and, after an incubation period of 20 minutes at 37° C., is stopped by adding 1 ml of glucose dehydrogenase reagent (1 small bottle of lyophilised glucose dehydrogenase/mutarotase mixture ("MERCK 14053") and 331.7 mg of β-nicotinamide-adenine dinucleotide (free acid "BOEHRINGER" degree of purity I) dissolved in 250 ml of 0.5M tris buffer, pH 7.6). In order to determine the glucose concentration, the mixture is incubated at 37° C. for 30 minutes and finally is measured photometrically at 340 nm against a reagent blank (containing enzyme but without sucrose).

The calculation of the inhibitory activity of inhibitors is made difficult by the fact that even slight changes in the test system, for example a 100% value which varies slightly from determination to determination, can have a significant effect on the test result which cannot be ignored. These difficulties may be avoided by running a standard with every determination; a saccharase inhibitor of the formula $C_{25}H_{43}O_{18}N$ which has a specific inhibitory activity of 77,700 SIU/g and, when employed in the test in amounts of 10 to 20 ng, leads to an inhibition of the order of size specified above, is conveniently used as the standard. If the difference between the extinctions at 340 nm of the 100% value and of the batch inhibited by the standard is known, the specific inhibitory activity of the inhibitor, expressed in saccharase inhibitor units per gram (SIU/g), can be calculated in a known manner from the extinction difference between the 100% value and the batch inhibited by the

sample solution, taking into consideration the amount of inhibitor employed.

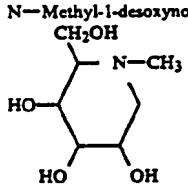
Specific saccharase-inhibitory activity in vitro

1-Desoxynojirimycin: 465,000 SIU/g
N-Methyl-1-desoxynojirimycin: 2,330,000 SIU/g

PREPARATION EXAMPLES

EXAMPLE 1

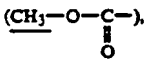
N—Methyl-1-desoxynojirimycin



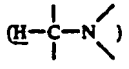
3.2 g of 1-desoxynojirimycin and 2 ml of 30% strength aqueous formaldehyde are added to 4 ml of 98% strength formic acid, whilst cooling with ice. The mixture is then heated under reflux for 8 hours. After cooling, the reaction mixture is diluted with acetone. A resinous precipitate separates out. The acetone solution is decanted off and the resin is rinsed several times with acetone. The residue is then dissolved in distilled water and the solution is freed from formic acid by adding a basic ion exchanger in the $^{\theta}OH$ form (Amberlite JRA 410). The ion exchanger is filtered off and the aqueous solution is brought to dryness under reduced pressure. 3.0 g of resinous N-methyl-1-desoxynojirimycin remain. The compound can be further purified by chromatography on cellulose. Water-containing butanol is used as the running agent. The compound may be cristallized from ethanol. M.P.: 153° C.

Mass spectrum: The most important peak in the upper mass range is at m/e=146 (M—CH_2OH).

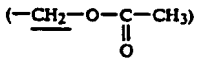
For further characterization, the compound is converted into the peracetylated compound, N-methyl-2,3,4,6-tetra-O-acetyl-1-desoxynojirimycin, with acetic anhydride/pyridine 1:1 at room temperature. A proton magnetic resonance spectrum of this derivative in $CDCl_3$ was measured at 100 MHz: 4 singlets for the total of 12 protons, which correspond to the methyl groups of the O-acetyl groups



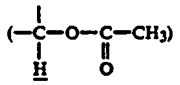
are found between δ=2.0 and 2.1 ppm. The methyl group bonded to N(CH_3—N<) is found as a singlet at δ=2.45 ppm. Two protons on a C atom bonded to nitrogen



absorb as poorly resolved multiplets between δ=2.1 and 2.5 ppm. A further proton of this type appears as a doublet of a doublet (J_1=11 Hz; J_2=4 Hz) at δ=3.18 ppm. A methylene group



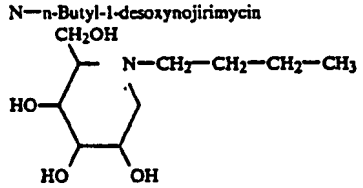
absorbs as an AB system at δ=4.16 and δ=4.22 ppm. The remaining three protons



are round as a multiplet between =4.9 and 5.2 ppm.

EXAMPLE 2

N—n-Butyl-1-desoxynojirimycin



12.4 ml of n-butylraldehyde, 0.01 mols of methanolic HCl and 1.5 g of $NaCNBH_3$ are added successively to 3.2 g of 1-desoxynojirimycin (0.02 mol) in 40 ml of absolute methanol, whilst cooling with ice and stirring. The reaction mixture is stirred at room temperature for 12 hours. It is then concentrated to dryness on a rotary evaporator. The residue is dissolved in 50 ml of water and extracted 3 times with 30 ml of $CHCl_3$ each time. The aqueous phase is again brought to dryness, the residue is taken up in 30 ml of H_2O and the solution is discharged onto a column 50 cm long and 2 cm wide which is filled with a strongly basic ion exchange resin in the OH^{θ} form (Amberlite IRA 400 or Dowex 1×2).

The reaction product is eluted with water and the individual fractions are investigated by thin layer chromatography. (Silica gel plates; running agent: ethyl acetate/methanol/water/25% strength ammonia 100:60:40:2; spray reagent: $KMnO_4$ solution). The fractions which contain N-n-butyl-1-desoxynojirimycin are collected and the aqueous solution is concentrated on a rotary evaporator. Acetone is added to the residue, whereupon crystallization occurs.

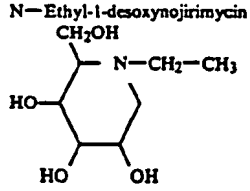
The crystals are filtered off, rinsed briefly with acetone and dried. 3 g of N-n-butyl-1-desoxynojirimycin of melting point 126°–127° C. are obtained.

Mass spectrum: The most important peaks in the upper mass range are found at m/e=188 (M-CH_2OH) and m/e=176 (M-CH_2-CH_2-CH_3).

In the case of less reactive aldehydes, a molecular sieve 3 Å was added to the reaction mixture in order to bind the water of reaction.

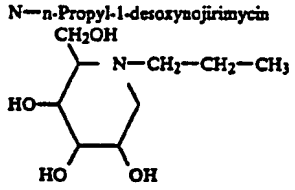
The following compounds were prepared by methods analogous to those of the above procedure:

N—Ethyl-1-desoxynojirimycin



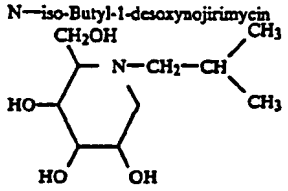
Mass spectrum: Intense peak at m/e=160 (M-CH_2OH).

N—n-Propyl-1-desoxynojirimycin

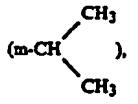


Mass spectrum: Intense peak at m/e=174 (M-CH_2OH). Peaks also at m/e=206 (M+H) and m/e=204 (M-H).

N—iso-Butyl-1-desoxynojirimycin

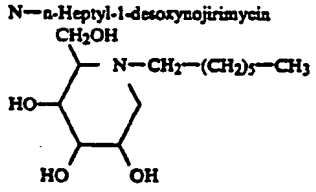


Mass spectrum: The most important peaks in the upper mass range are found at m/e=188 (M-CH_2OH), m/e=176



m/e=220 (M+H) and m/e=218 (M-H).

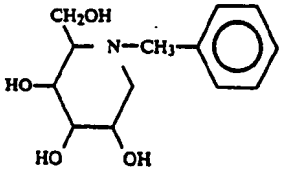
N—n-Heptyl-1-desoxynojirimycin



Melting point: 111°–113° C. (from acetone).

Mass spectrum: The most important peak in the upper mass range is at m/e=230 (M-CH_2OH). Peaks are also found at me/=262 (M+H) and 260 (M-H).

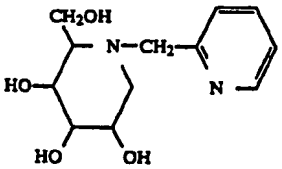
N—Benzyl-1-desoxynojirimycin



Melting point: 183°–184° C. (from methanol).

Mass spectrum: The most important peak in the upper mass range is found at m/e=222 (M-CH_2OH).

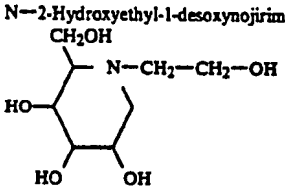
N—(2-Pyridyl)-methyl-1-desoxynojirimycin



Melting point: 174°–175° C. (from ethanol).

Mass spectrum: The most important peaks in the upper mass range are found at m/e=255 (M+H), m/e=236 (M-H_2O) and m/e=223 (M-CH_2OH).

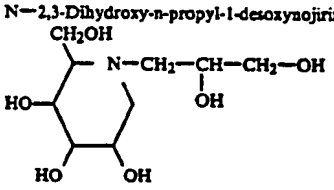
N—2-Hydroxyethyl-1-desoxynojirimycin



Melting point: 114° C. (from ethanol).

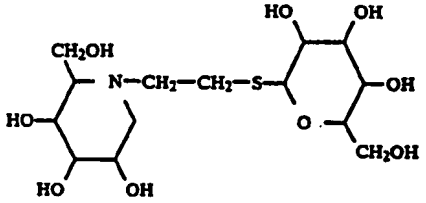
Mass spectrum: The most important peak in the upper mass range is at m/e=176 (M-CH_2OH).

N—2,3-Dihydroxy-n-propyl-1-desoxynojirimycin

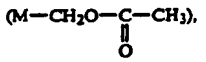


Mass spectrum: The most important peaks in the upper mass range at at m/e=206 (M-CH_2OH) and m/e=176. The substance is a mixture of two diastereomeric compounds.

N—(S-β-D-Glucopyranosyl-2-mercaptoethyl)-1-desoxynojirimycin



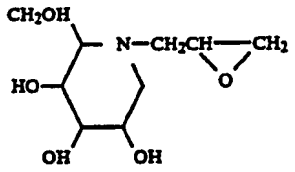
Mass spectrum: The mass spectrum of the compound peracetylated in pyridine/acetic anhydride was measured. The most important peaks in the upper mass range are found at m/e=648



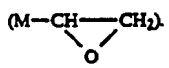
m/e=588 and m/e=344.

The aldehyde required for the reaction was obtained from O-acetylated 1-thioglucose and chloroacetaldehyde. The acetyl groups in the end product were split off by transesterification with catalytic amounts of $NaOCH_3$in MeOH.

N—Oxiranyl-methyl-1-desoxynojirimycin

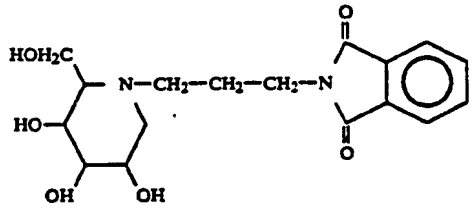


Mass spectrum: The most important peaks in the upper mass range are found at m/e=219 (M), m/e=202, m/e-188 (M-CH_2OH) and m/e=176



The substance is a mixture of two diastereomeric compounds.

N—(3-N—Phthalimido-n-propyl)-1-desoxynojirimycin

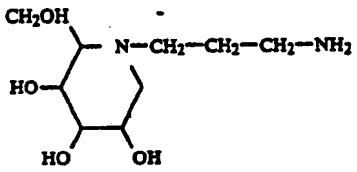


Mass spectrum: The most important peaks in the upper mass range were found at m/e=348, m/e=319 (M-CH_2OH), m/e=301, m/e=200, m/e=188, m/e=174, m/e=160 and m/e=147.

In this case, chromatography on a basic ion exchange resin was dispensed with and the compound was purified by boiling up with acetone and recrystallisation from ethanol.

Melting point: 208°–210° C.

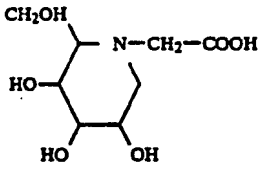
N—(3-Amino-n-propyl)-1-desoxynojirimycin



Mass spectrum: The most important peaks in the upper mass range are at m/e=189 (M-CH_2OH) and m/e=146.

The compound was obtained from the above phthalimido compound by hydrazinolysis in methanol.

N—(1-Desoxynojirimycin-yl)-acetic acid

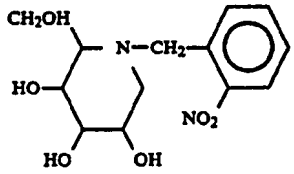


Mass spectrum: The most important peaks in the upper mass range are found at m/e=203 (M-H_2O), m/e=159, m/e=145 and m/e=100.

The compound was not purified by chromatography over a basic ion exchange resin but by recrystallization from methanol/water.

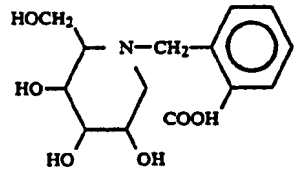
Melting point: 187°–188° C.

N—o-Nitrobenzyl-1-desoxynojirimycin



Rf value: 0.85 (on thin layer chromatography ready-to-use silica gel 60 plates from Messrs. Merck; running agent: ethyl acetate/methanol/H_2O/25% strength ammonia 100:60:40:2). For comparison: Rf value of 1-desoxynojirimycin: 0.3.

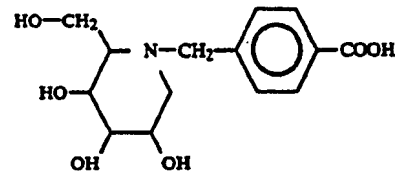
N—o-Carboxybenzyl-1-desoxynojirimycin



Rf value: 0.7 (plates and running agent as indicated for the above compound).

For purification, the compound was chromatographed over a basic ion exchange resin as indicated above, but finally was eluted with 1% strength acetic acid.

N—p-Carboxybenzyl-1-desoxynojirimycin

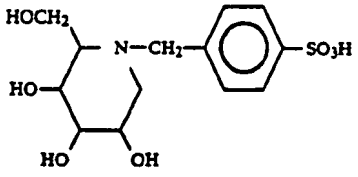


m.p.: 280°–281° C. (from H_2O/methanol).

Rf value: 0.7 (plates and running agent as indicated above).

In this case also, the compound was eluted from the basic ion exchange resin with 1% strength acetic acid.

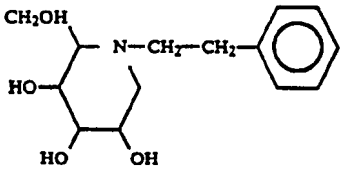
N—p-Sulfobenzyl-1-desoxynojirimycin



4.8 g of benzaldehyd-4-sulfonic acid, 1.8 ml of acetic acid and 0.8 g of $NaCNBH_3$ are added to 2 g of 1-desoxy-nojirimycin in 40 ml methanol. The mixture was refluxed for 4 hours and stirred for 12 hours at room temperature. The precipitate was filtered off and recrystallized from water. 1.2 g of N-p-sulfobenzyl-1-desoxynojirimycin of melting point ~320° C. (dec.) are obtained.

EXAMPLE 3

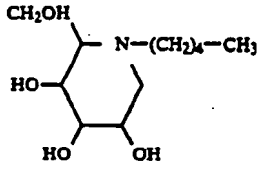
N—β-Phenylethyl-1-desoxynojirimycin



3 g of phenylacetaldehyd and 0.8 g of $NaCNBH_3$ are added to 2 g of 1-desoxynojirimycin and 1.8 ml acetic acid in 40 ml of methanol. The mixture is stirred for 12 hours at room temperature and evaporated on a rotary evaporator. The residue is dissolved in ethanol/water (2:1) and discharged onto a column which is filled with a strongly acidic ion exchange resin in the $H^{\oplus}$-form. The column is washed with 2 l of ethanol and water (2:1). Then the product is eluted with ethanol/2% strength aqueous ammonia (2:1). The fractions are investigated by thin layer chromatography and those which contain the product are collected and dried. The residue is crystallized from 100 ml ethanol. 2.5 g of N-β-phenyl-ethyl-1-desoxynojirimycin with a melting point 179°–181° C. are obtained.

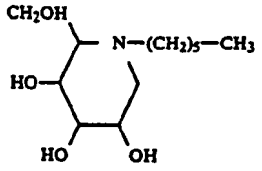
The following compounds were prepared analogously:

N—n-Pentyl-1-desoxynojirimycin



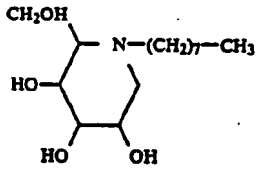
m.p. 97° C. (from acetone).

N—n-Hexyl-1-desoxynojirimycin



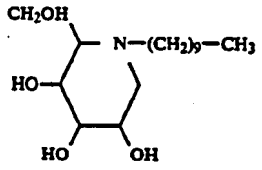
m.p. 112°–113° C. (from ethanol/acetone).

N—n-Octyl-1-desoxynojirimycin



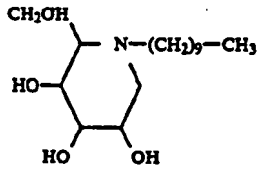
m.p. 115°–117° C. (from ethanol/acetone).

N—n-Nonyl-1-desoxynojirimycin



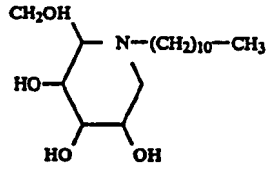
m.p. 105°–107° C. (from ethanol/acetone).

N—n-Decyl-1-desoxynojirimycin



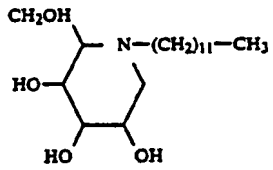
m.p. 151° C. (sinters at 91° C. from MeOH/acetone).

N—n-Undecyl-1-desoxynojirimycin



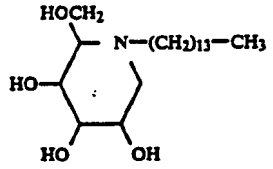
m.p. 162° C. (sinters at 91° C. from ethanol/acetone).

N—n-Dodecyl-1-desoxynojirimycin



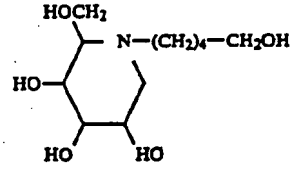
m.p. 164° C. (sinters at 97° C. from ethanol/acetone).

N—n-Tetradecyl-1-desoxynojirimycin



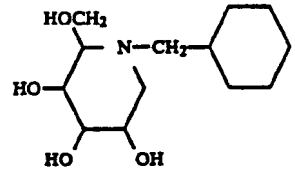
m.p. 105°–107° C. (from methanol).

N—n(5'-Hydroxypentyl)-1-desoxynojirimycin



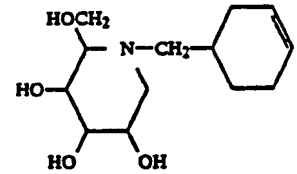
m.p. 86°–87° C. (from butanol).

N—Cyclohexylmethyl-1-desoxynojirimycin



m.p. 138°–140° C. (from acetone).

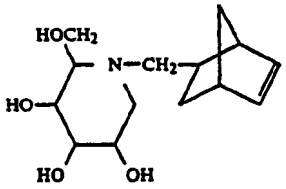
N—(3'-Cyclohexenylmethyl)-1-desoxynojirimycin



m.p. 142°–144° C. (from acetone).

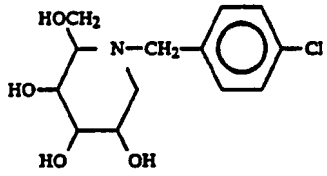
N—(2'-Norbornen-5'-yl-methyl)-1-desoxynojirimycin

-continued



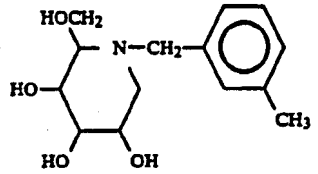
m.p. 160°–162° C. (from ethanol).

N—p-Chlorbenzyl-1-desoxynojirimycin



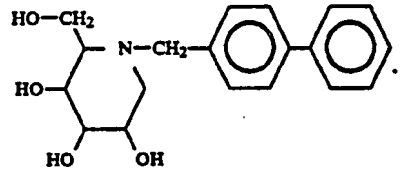
m.p. 153°–155° C. (from acetone).

N—m-Methylbenzyl-1-desoxynojirimycin



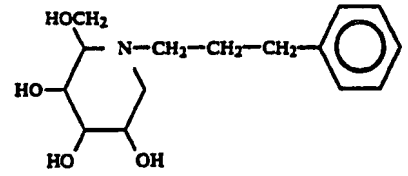
m.p. 134°–136° C. (from methanol).

N—(p-Biphenylmethyl)-1-desoxynojirimycin



m.p. 240°–245° C. (from water/ethanol).

N—(n-3'-phenylpropyl)-1-desoxynojirimycin

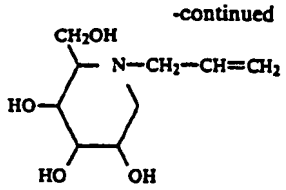


m.p. 125°–127° C. (from ethanol).

EXAMPLE 4

N—Allyl-1-desoxynojirimycin

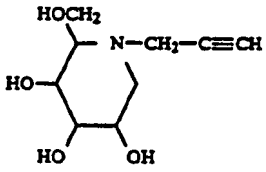
-continued



5 g of 1-desoxynojirimycin, 5 g of Ag_2O and 5 g of Allylbromide are stirred in 30 ml of dimethylformamide and 30 ml of water for 3 hours at room temperature. The silver salts are filtered off and the filtrate is evaporated at the rotary evaporator. The residue is recrystallized from ethanol. 4.5 g of N-allyl-1-desoxynojirimycin of melting point 131° to 132° C. are obtained.

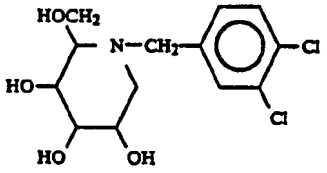
The following products are obtained analogously, the isolation and purification optionally carried out by chromatography on a strongly acidic ion exchange resin ($H^{\oplus}$-form).

N—Propargyl-1-desoxynojirimycin



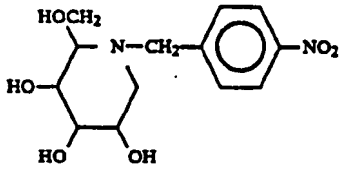
m.p. 160° C. (from acetone).

N—(3',4'-Dichlorobenzyl)-1-desoxynojirimycin



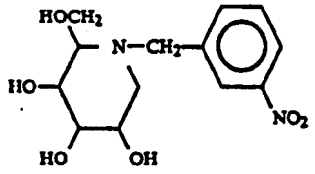
m.p. 130°–132° C.

N—(p-Nitrobenzyl)-1-desoxynojirimycin



m.p. 144°–146° C.

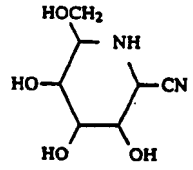
N—(m-Nitrobenzyl)-1-desoxynojirimycin



m.p. 168°–170° C.

EXAMPLE 5

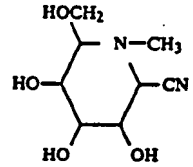
1-Cyano-1-desoxynojirimycin



17.5 g of nojirimycin bisulfite adduct are added to 200 ml of water and 21.2 of $Ba(OH)_2 \cdot 8\ H_2O$. The mixture is stirred for 1 hour and the solid is filtered off. 12 ml of liquid HCN are added to the filtrate and the mixture is stirred for 30 minutes. The solution is filtered and concentrated on the rotary evaporator to 20 ml. 20 ml of methanol are added whereby the crystallization of the product starts. 100 ml of ethanol are added to complete crystallization. After filtration 12.0 g of 1-cyano-1-desoxynojirimycin are obtained m.p. 155°–156° C. (from methanol/water).

EXAMPLE 6

N—Methyl-1-cyano-1-desoxynojirimycin

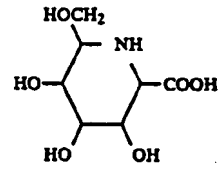


The compound is obtained from 1-cyano-1-desoxynojirimycin with 35% strength aqueous formaldehyd solution and $NaCNBH_3$ in methanol according to example 3.

Mass spectrum: The most important peaks in the upper mass range are at m/e=171 (M—CH_2OH), m/e=157 and m/e=144.

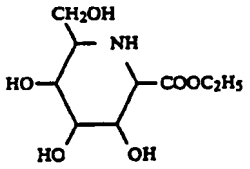
EXAMPLE 7

1-Desoxynojirimycin-1-carboxylic acid



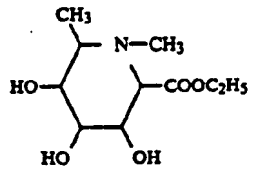
10 g of 1-cyano-1-desoxynojirimycin are refluxed with 5 g of sodium hydroxide in 100 ml of water for one hour. Hydrochloric acid is added up to pH 4. The mixture is dried on the rotary evaporator and the residue is extracted with hot methanol, sodium chloride is separated and the methanolic solution is evaporated. The residue is recrystallized from water and water/methanol. 10.5 g of 1-desoxynojirimycin-1-carboxylic acid of m.p. 268°–270° C. are obtained.

EXAMPLE 8



7 g of 1-desoxynojirimycin-1-carboxylic acid are refluxed with 100 ml of ethanolic hydrochloric acid for 2 hours and evaporated at the rotary evaporator. The residue is treated with ethanol and ethanolic ammonia. The solution was filtered and concentrated. 8 g of 1-desoxynojirimycin-1-carboxylic acid ethyl ester are obtained. NHR-Spectrum 100 MHz: triplet at $\sigma=1.3$ ppm (3H, —COO—CH_2—CH_3); multiplet at $\sigma=2.4$–2.6 ppm (1H, >N—CH<CH_2OH); multiplet at $\sigma=3.2$–3.5 ppm (4H); multiplet at $\sigma=2.6$–3.9 ppm (2H, —CH_2—OH); quartet at $\sigma=4.25$ ppm (2H, —COO—CH_2—CH_3).

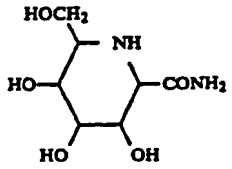
EXAMPLE 9



From 1-desoxynojirimycin-1-carboxylic acid ethyl ester according to example 6.

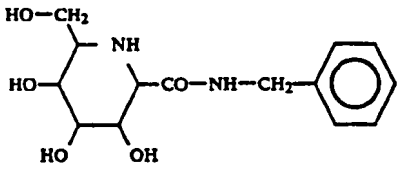
Mass spectrum: The most important peaks in the upper mass range are at m/e=218 (M—CH_2OH), m/e=200, m/e=176, m/e=158 and m/e=126.

EXAMPLE 10



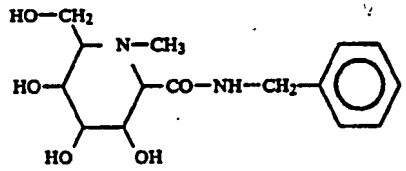
6 g of 1-desoxynojirimycin-1-carboxylic acid ethyl ester are refluxed in 90 ml of 25% strength aqueous ammonia for one hour. After cooling to room-temperature the solution is treated with ethanol and the precipitate (ammonium salt of 1-desoxynojirimycin-1-carboxylic acid) is separated off. The filtrate is concentrated, treated with water and chromatographed with a column filled with a strongly basic ion exchange resin ($OH^{\ominus}$-form). The product is eluted with water. The fractions containing the carbonamide are collected and concentrated. The residue is recrystallized from ethanol and 3 g of 1-desoxynojirimycin-1-carboxylic acid amide, m.p. 175°–176° C., are obtained.

EXAMPLE 11



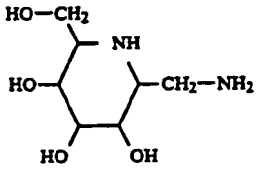
500 mg of 1-desoxynojirimycin-1-carboxylic acid ethyl ester are refluxed for 5 minutes in 1 ml of benzylamine. The mixture after cooling is treated several times with ether and the solvent decanted off. The residue is recrystallized from methanol and 400 mg of 1-desoxynojirimycin-1-carboxylic acid benzylamide, m.p. 221°–222° C. are obtained.

EXAMPLE 12



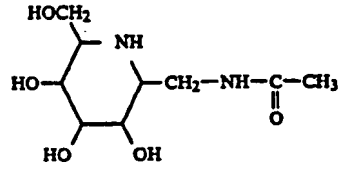
From 1-desoxynojirimycin-1-carboxylic acid benzylamide according to example 6; m.p. 229°–230° C. (from methanol).

EXAMPLE 13



5 g of 1-cyano-1-desoxynojirimycin are hydrogenated in 100 ml of water with 10 g of Raney-Nickel and a pressure of 3.5 bar hydrogen. The catalyst is filtered off and the solution is dried on the rotary evaporator. The residue is treated with some hot methanol, filtered and evaporated. The residue is recrystallized from methanol to yield 3.4 g of 1-aminomethyl-1-desoxynojirimycin, m.p. 154°–155° C.

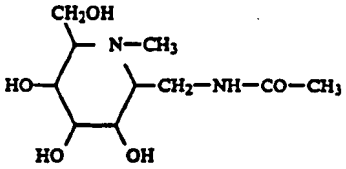
EXAMPLE 14



3.8 g of 1-aminomethyl-1-desoxynojirimycin in 40 ml methanol/water (1:1) are treated at 0° C. with 3 ml of acetic acid anhydride and stirred for 15 minutes at 0° C. and 30 minutes at room temperature. The solution was evaporated. The residue is treated with 60 ml of water and neutralized with a basic ion exchange resin ($OH^{\ominus}$-form). After removal of the resin the solution is dried

and recrystallized twice from ethanol. 3 g of 1-acetamidomethyl-1-desoxynojirimycin are obtained, m.p. 169°-171° C.

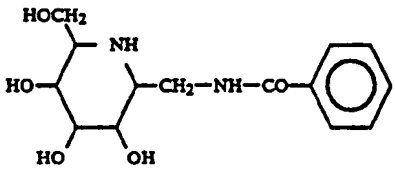
EXAMPLE 15



the compound is prepared from 1-acetamido-methyl-1-desoxynojirimycin analogously to example 6.

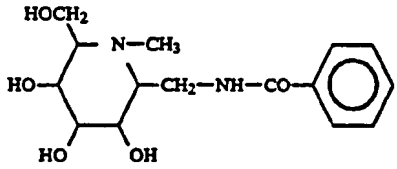
Mass spectrum: the most important peaks in the upper mass range are at m/e=176 and m/e=158.

EXAMPLE 16



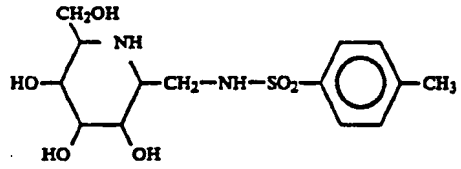
the compound is prepared from 1-aminomethyl-1-desoxynojirimycin and benzoylchloride according to example 14; m.p. 216° C. (from methanol).

EXAMPLE 17



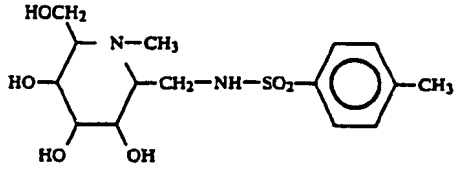
the compound is prepared from 1-benzoylamino-1-desoxynojirimycin according to example 6; m.p. 135°-136° C. (from butanol).

EXAMPLE 18



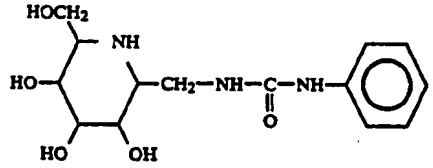
960 mg of 1-aminomethyl-1-desoxynojirimycin are refluxed with 1 g of tosylchloride in 10 ml of methanol/water (1:1) for 3 hours. The solvent was distilled off in vacuo and the residue treated with acetone. The solid is filtered off, dissolved in water and neutralized with a basic ion exchange resin. After removal of the resin the solution is evaporated and residue recrystallized from water. 600 mg 1-tosylaminomethyl-1-desoxynojirimycin of m.p. 173°-175° C. are obtained.

EXAMPLE 19



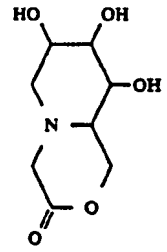
the compound is prepared from the compound of example 18 according to example 6; m.p. 218°-219° C. (from water).

EXAMPLE 20



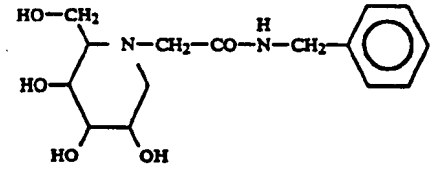
960 mg of 1-aminomethyl-1-desoxynojirimycin are stirred for 15 minutes with 0,8 ml of phenylisocyanate in 10 ml methanol/water (1:1) at −20° C. The mixture is slowly warmed to room temperature and the solvent is distilled off. The residue is discharged onto a column filled with cellulose and the product is eluted with butanol/water (9:1). The fractions containing the product are collected and concentrated. The residue is recrystallized from ethanol and 400 mg of m.p. 161°-162° C. are obtained.

EXAMPLE 21



5 g of N-(1-desoxynojirimycinyl)-acetic acid are refluxed in 50 ml of dimethylformamide for 30 minutes. The solvent is removed in high vacuo and the remaining oil crystallized from ethanol. 3.5 g of the compound of m.p. 157°-159° C. are obtained.

EXAMPLE 22



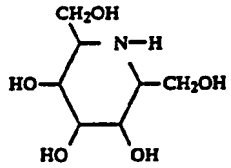
500 mg of the compound of example 21 are refluxed with 1 ml of benzylamine in 20 ml of dimethylformamide for 6 hours. The solvent is removed in high vacuo

and the residue recrystallized from ethanol/acetone (1:2). 400 mg of m.p. 129° C. are obtained.

N-(1-Desoxynojirimycinyl)-acetic acid n-butylamide is prepared analogously.

Mass spectrum: The most important peaks in the upper mass range are: m/e=245, m/e=203, m/e=176, m/e=159 and m/e=145.

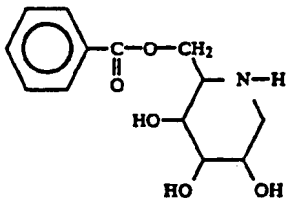
EXAMPLE 23



A suspension of 2.3 g of 1-desoxynojirimycin-1-carboxylic acid ethyl ester in 50 ml of abs. tetrahydrofuran (THF) are added to 1.9 g of $LiAlH_4$ in 50 ml of abs. THF. The mixture is stirred for one hour and then refluxed for 5 hours. 20 ml of ethyl acetate, 2 ml of water and 4 ml of 15% strength KOH are added dropwise. The precipitate is filtered off and extracted by a water-methanol mixture. The solvent is distilled off and the residue extracted with methanol. The methanol solution is concentrated and the residue discharged with water onto a column filled with a strongly acidic ion exchange resin ($H^{\oplus}$-form). The column is eluted first with water and then with 0,25% strength aqueous ammonia. The fractions containing the product are collected and freed from the solvent. 500 mg of the compound are obtained.

Mass spectrum: The most important peak in the upper mass range is at m/e 162. Smaller peaks are m/e=144 and m/e 102.

EXAMPLE 24

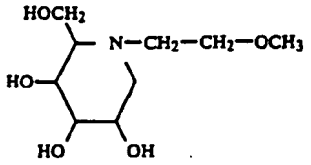


3.5 g of pulverized K_2CO_3 and 2.0 g of benzoylchloride are added to 2.1 g of 1-desoxynojirimycin in 40 ml of acetone and 15 ml of water. The mixture is stirred for 3 hours at 40° C. and for 12 hours at room temperature. The salts are filtered off and the solvent is removed in vacuo. The residue is chromatographed on a silica gel column and eluted first with ethylacetate/methanol (10:4) and then with ethylacetate/methanol/water/ammonia (10:4:0.5:0.02). Each 10 ml of eluate were obtained separately and fractions 51 to 57 contained the desired product (350 mg of m.p 160° C.)

EXAMPLE 25

N—(β-Methoxyethyl)-1-desoxynojirimycin

-continued

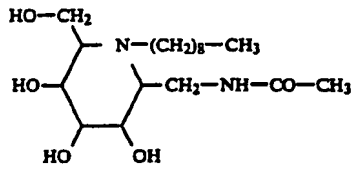


5.2 g o β-methoxyacetaldehyd-dimethylacetal in 15 ml of water and 5 ml of methanol are treated with 0.6 ml of HCl for 48 hours at room temperature and 6 hours at 60° C. Then 1.6 g of 1-desoxynojirimycin and 0.7 g of $NaCNBH_3$ are added at room temperature. The mixture is kept for 12 hours at 50° C. The solvent is removed in vacuo, the residue together with water is discharged onto a column which is filled with a strongly acidic ion exchange resin. The column is eluted first with water and then with 2% strength ammonia. The fractions containing the product are collected and concentrated. The residue is chromatographed on a cellulose-column with butanol/water (9:1). 1.2 g of the compound are obtained with a Rf-value: 0.57 (on thin layer chromatography ready-to-use silica gel 60 plates from Messrs. Merck; running agent: ethyl acetate/methanol/-H_2O/25% strength ammonia 100:60:40:2). For comparison Rf-value of 1-desoxynojirimycin: 0.3.

Analogously are obtained N-(β-methylmercaptoethyl)-1-desoxynojirimycin (MS: Most important peaks in the upper mass range are at m/e=220, m/e=206 and m/e=176), N-(β-ethylmercapto-ethyl)-1-desoxynojirimycin (MS: Most important peaks in the upper mass range are at m/e=220 and m/e=176) and N-[β-(β-methoxy)-ethoxyethyl]-1-desoxynojirimycin (MS: Most important peaks in the upper mass range are at m/e=234 and m/e=176.

EXAMPLE 26

N—n-Nonyl-1-acetaminomethyl-1-desoxy-nojirimycin

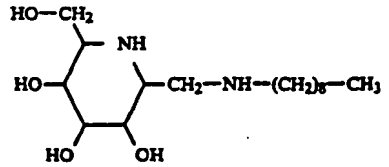


the compound is obtained from 1-acetamino-1-desoxynojirimycin according to example 3.

MS: Most important peaks in the upper mass range are at m/e 329, , m/e=288, m/e=270 and m/e 258.

EXAMPLE 27

1-n-Nonylaminomethyl-1-desoxynojirimycin



1.2 ml of acetic acid, 1.56 ml of nonylaldehyd and 0.7 g of $NaCNBH_3$ are added to 1.9 g of 1-aminomethyl-1-desoxynojirimycin in 40 ml methanol at 0° C. The mix-

ture is stirred for 1 hour at 0° C. and 12 hours at room temperature. The solvent is distilled off in vacuo and the residue is slurried in water, discharged onto a column filled with a strongly acidic ion exchange resin ($H^{\oplus}$-form) and eluted first with ethanol/water (1:1), then with 0.3% strength aqueous ammonia and finally with ethanol/0.6% strength aqueous ammonia (1:1). The fractions containing the product are collected and concentrated. 1 g of the compound with Rf-value 0.52 (plate and running agent as in ex. 25) are obtained.

EXAMPLE 28

N-Methylnojirimycin hydrochloride

57 ml of chloroformic acid ethylester dissolved in 360 ml of absolute THF are added dropwise to a solution of 294 g of 3-O-benzyl-6-O-triphenylmethyl-1.2-isopropylidene-5-amino-6-desoxy-α-D-glucofuranose in 800 ml of absolute THF and 83.6 ml of triethylamine at 0° C. The mixture is stirred for 2 hours at 20° C., filtered to remove precipitated salt and concentrated. The product is put into ethyl acetate, twice extracted with water, dried and concentrated. 318.6 g of crude 3-O-benzyl-6-O-triphenylmethyl-1.2-O-isopropylidene-5-ethoxycarbonylamino-5-desoxy-α-D-glucofuranose are obtained as a yellow oil.

174.7 g of this oil are dissolved in 340 ml of absolute ether and added dropwise into a suspension of 39 g $LiAlH_4$ in 690 ml of abs. ether at 10° to 15° C. The mixture is refluxed for 5 hours and while cooled with ice treated with 520 ml of ethyl acetate, 40 ml of water and 78.5 15% strength aqueous KOH. The mixture is filtered to be freed from solids, washed with ether and evaporated in vacuo. 144.2 g of 3-O-benzyl-6-O-triphenylmethyl-1.2-iso-propylidene-5-methylamino-5-desoxy-α-D-glucofuranose are obtained as a yellow oil.

This crude product is dissolved in 165 ml of abs. THF and added dropwise at −70° C. into a mixture of 24.6 g of metallic sodium in 820 ml liquid ammonia. Further 2.5 g of sodium is added and the mixture is stirred for 2 hours. Still at −70° C. 91 g of ammonium chloride is added in portions. The mixture is allowed to warm to room temperature within 12 hours. The suspension is stirred into 500 ml of methanol. The solids are filtered off and the filtrate is concentrated. The residue is treated with water/chloroform and the phases are separated. The aqueous phase is concentrated and the crude product is purified by means of a cation exchange resin. After recrystallization from ethyl acetate 14.8 g of 5-methylamino-5-desoxy-1.2-O-iso-propylidene, m.p. 124°–126° C. are obtained.

(b) Preparation of the final product A solution of 470 mg of the product obtained according to example 28 (a) in 2 ml of hydrochloric acid is kept at 0° C. for 16 hours. The mixture is concentrated at 20° C. in vacuo and twice dissolved in water and evaporated in vacuo.

The amorphous N-methylnojirimycin-hydrochloride shows a three times stronger effect in the saccharase inhibition test than 1-desoxy-nojirimycin.

EXAMPLE 29

N-Phenyl-1-desoxynojirimycin

(a) Preparation of the starting material

20 g of 1-O-acetyl-2.3-O-isopropylidene-6-p-toluenesulfonyl-α-L-sorbofuranose are heated together with 30 ml of aniline for 5 hours to 110° C. After cooling, 200 ml of ethyl acetate are added and the solids are filtered off. The solution is concentrated in vacuo and excess aniline is removed in high vacuo. The residue is purified by chromatography with a cation exchange resin. After recrystallisation from ethyl acetate/petroleum ether 3.0 g of 6-phenylamino-2.3-O-isopropylidene-6-desoxy-α-L-sorbofuranose, m.p. 156° C., are obtained,

(b) Preparation of the final product

1.0 g of the product obtained according to example 29(a) are dissolved in 4 ml of 6 n HCl and kept for 24 hours at 0° C. Then 6 ml water are added and the pH is adjusted to 6–7 with 3 ml triethylamine. 1 g Raney-nickel is added and the product is hydrogenated under a H_2-pressure of 3.5 bar. The catalyst is filtered off and the solvent is removed. The product is purified by means of column filled with a cation exchange resin. 470 mg of a slightly yellow oil are obtained.

MS: most important peaks in the upper mass range are at m/e=239, m/e=208 and m/e=148.

EXAMPLE 30

N-Cyclohexyl-1-desoxynojirimycin

Method A

2 g of 1-desoxynojirimycin are dissolved in 40 ml of abs. methanol and 1.8 ml glacial acetic acid and treated first with 5.2 ml cyclohexanone and then with 3.4 g of $NaCNBH_3$. This mixture is refluxed for 96 hours, cooled and concentrated in vacuo. The residue is treated with methanol/water (1:1) and purified by a column filled with a cation exchange resin ($H^{\oplus}$-form). 1.9 g pure product are obtained with a Rf-value of 0.58 (thin layer chromatography 60/F 254 plates of Messrs. Merck, running agent: ethyl acetate/methanol/-water/25% strength aqueous ammonia 120:70:10:1); for comparison: Rf-value of 1-desoxynojirimycin is 0.13.

Method B

1 g of 6-cyclohexylamino-2.3-O-isopropylidene-6-desoxy-α-L-sorbofuranose (prepared according to example 29(a)) is kept for 40 hours in a mixture of 6 ml of methanol/6 n HCl (1:1) at 0° C., treated with 10 ml of water and 3.0 ml of triethylamine and hydrogenated for 2 hours with 3.5 bar H_2 and PtO_2 as the catalyst. The catalyst is filtered off, the solution evaporated in vacuo and purified by a column filled with cation exchange resin. 610 mg of the compound are obtained, identical with the compound prepared according to method A.

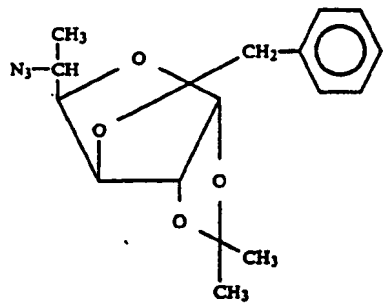
N-Isopropyl-1-desoxynojirimycin (Rf-value=0.45) is prepared analogous to method A.

N-(1-Methyldecyl)-1-desoxynojirimycin (mixture of diastereomers, Rf-value 0.79 and 0.86) is prepared analogous to method A.

EXAMPLE 31

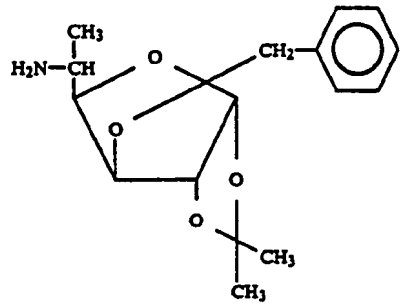
1.6-Didesoxynojirimycin

(a) 5-Azido-3-O-benzyl-5.6-didesoxy-1.2-O-isopropylidene-α-D-glucofuranose



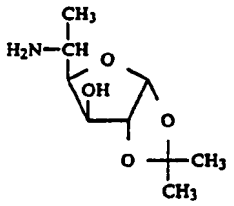
186 g of 3-O-benzyl-6-desoxy-1.2-O-isopropylidene-5-O-methylsulfonyl-β-L-idofuranose, 500 ml of dimethylsulfoxide and 65 of NaN_3 are heated 5 hours under nitrogen at 120°–125° C. After cooling the mixture is poured into ice-water, extracted three times with petroleum ether, the organic phase washed with water, dried and evaporated. 156 g of crude product is obtained as an oil. 1H-NMR(100 MHz, C_6D_6):δ=7.15 (m, 5H), 5.72 (d, J=4 Hz, 1H), 1.32 (s, 3H), 1.17 (d,J=6 Hz, 3H), 1.06 ppm (s, 3H).

(b) 5-Amino-3-O-benzyl-5.6-didesoxy-1.2-O-isopropylidene-α-D-glucofuranose



100 g of the crude product of example 31(a) in 200 ml of anhydrous THF are added dropwise to 6 g of $LiAlH_4$ in 250 ml of anhydrous THF. The mixture is stirred for 15 hours and refluxed for 1 hour. While cooling 6 ml of water and 18 ml of 15% strength aqueous KOH are added dropwise. The mixture is stirred for further 15 hours, the precipitate is filtered off and the solvent is removed. The residue is treated with 500 ml of ether and twice extracted with 100 ml of 2 n HCl. The aqueous phase is rendered alkaline by means of 45% strength aqueous NaOH and extracted three times with 200 ml ether. After drying the organic phase the solvent is distilled off and 62.5 g of the compound are obtained as a yellow oil. 1H-NMR (100 MHz, $CDCl_3$):δ=7.3 (m, 5H), 5.8 (d,J=4 Hz, 1H), 5.70 (d, J=12 Hz, 14), 5.58 (d, J=4 Hz, 1H), 5.42 (d, J=12 Hz, 14), 3.98 (d, J=4 Hz, 1H), 1.45 (s, 3H), 1.30 (s, 3H) 1.15 ppm (d,J=6 Hz, 3H).

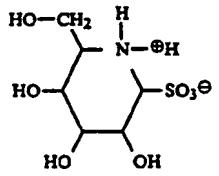
(c) 5-Amino-5.6-didesoxy-1.2-O-isopropylidene-α-D-glucofuranose



50 g of the compound obtained according to example 31 (b) are hydrogenated in 1 l methanol in the presence of 10 g of Pd on charcoal (5% strength) at 60° C. for 5 hours with a pressure of 70 bar hydrogen. The catalyst is filtered off and the solvent removed in vacuo. 25.7 g of the compound are obtained.

1H-NMR (100 MHz, compound dissolved in $CDCl_3$ and extracted with D_2O):δ=5.97 (d, J=4 Hz, 1H), 4.50 (d, J=4 Hz, 1H), 4.34 (d, J=4 Hz, 1H), 1.49 (s, 3H), 1.32 (s, 3H), 1.23 ppm (d, J=6 Hz, 3H).

(d) 5-Amino-5.6-didesoxy-D-glucose-1-sulfonic acid



10 g of the compound obtained according to example 31 (c) are suspended in 50 ml of water.

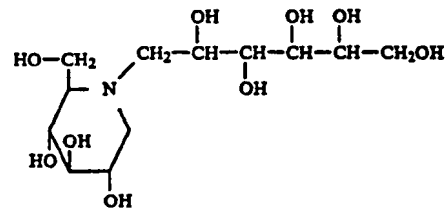
Sulfurdioxide is passed in for 15 hours. A clear solution originates which is warmed up to 60° C. After about 4 hours the compound starts to crystallize. 100 ml of methanol are added and the precipitated product is filtered off after 15 hours. 8.5 g of the compound are obtained, m.p. 180° C. (dec.)

(e) 1.6-Didesoxynojirimycin

10 g of the compound of example 31 (d) are hydrogenated in 120 ml of water in the presence of 13.3 g of $Ba(OH)_2.8H_2O$ and 10 g of Raney-Nickel for approximately 7 hours. The solids are filtered off and the solvent removed in vacuo. The remaining oil crystallizes after a short time and the compound is recrystallized from methanol to yield 5.3 g with m.p. 163°–164° C.

EXAMPLE 32

N—(1-Desoxyglucityl)-1-desoxynojirimycin



0.8 g of 1-desoxynojirimycin, 7.2 g of glucose, 40 ml of methanol, 10 ml of water, 1.5 ml glacial acetic acid and 1.3 g $NaCNBH_3$ are stirred together for 15 hours at room temperature. Then the mixture is refluxed for 6 hours, evaporated, treated with 10 ml 2 n HCl, warmed up to 40° C. until the generating of hydrogen ceases, discharged onto a column filled with an acidific ion exchange resin and washed with water. The product is

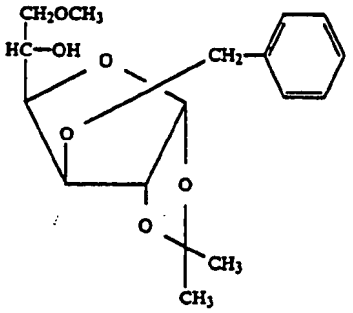
eluted with 0.3 n ammonia, the solvent distilled off in vacuo and the residue chromatographed on 100 g of silica gel (70–230 mesh) with methanol/conc. ammonia (10:5). 1 g of the compound is obtained.

Mass spectrum: m/e=296 (20%), 278 (15%) 176 (100%), 158 (30%), 132 (30%).

EXAMPLE 33

1-Desoxy-6-O-methylnojirimycin

(a) 3-O-Benzyl-1.2-O-isopropylidene-6-O-methyl-β-L-idolfuranose

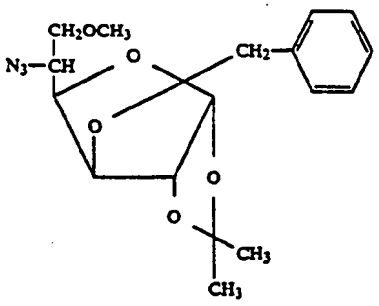


440 g of 5.6 -anhydro-3-O-benzyl-1.2-O-isopropylidene-β-L-idofuranose are refluxed in 1.5 l of methanol with 92 g of sodium methylate for 1 hour. After cooling the mixture is neutralized with glacial acetic acid, methanol is distilled off, the residue is discharged on to 300 ml of water and extracted with chloroform. After drying and evaporating 388 g of an oil are obtained.

(b) 3-O-Benzyl-1.2-O-isopropylidene-6-O-methyl-5-O-methylsulfonyl-β-L-idofuranose

384 g of the product of example 33 (a) in 300 ml of pyridine and 760 ml of chloroform are treated dropwise with 148 ml of mesylchloride at 0° C., and the mixture is stirred for 15 hours at room temperature. 200 ml of ice-water are added. The mixture is stirred for 20 minutes and extracted three times with 200 ml of chloroform. The organic phase is washed twice with deluted hydrochloric acid, with water and with 10% strength $NaHCO_3$-solution and dried. The solvent is removed in vacuo and the residue recrystallized from ethylacetate to yield 347 g to which further 26 g obtained from the mother liquors by filtration over 200 g of silica gel are added. 79% of theory; m.p. 133° C.

(c) 5-Azido-3-O-benzyl-5-desoxy-1.2-O-isopropylidene-6-O-methyl-α-D-glucofuranose



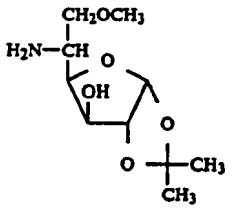
201 g of the product of example 33 (b), 500 ml of hexamethylphosphoric acid triamide and 65 g of sodium azide are heated for 15 hours to 100° to 110° C. under a nitrogen current. After cooling the mixture is poured on to ice-water, extracted four times with ethylether, the ethyl ether phases washed with diluted hydrochloric acid, water and $NaHCO_3$-solution, dried and evaporated in vacuo. 159 g (91% of theory) are obtained as an oil.

(d) 5-Amino-3-O-benzyl-5-desoxy-1.2-O-isopropylidene-6-O-methyl-α-D-glucofuranose

134.5 g of the product of example 33(c) in 200 ml anhydrous THF are added dropwise to 7.3 g of $LiAlH_4$ in 500 ml of anhydrous THF at room temperature. The mixture is stirred for 4 hours and kept over night. Then 7.3 ml of water are added dropwise, 22 ml 15% strength KOH are added and the mixture is stirred for 8 hours. The precipitate is filtered off, washed with THF and the filtrate is evaporated in vacuo.

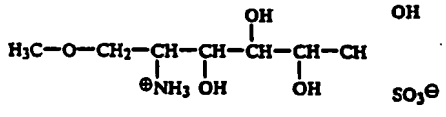
The obtained oil is covered with a layer of 300 ml of ethylether and treated under cooling at 0°–10° C. with 150 ml of 5N hydrochloric acid. The organic phase is separated and washed with hydrochloric acid. The aqueous phases are washed with ethyl ether. The aqueous phase is treated with 100 ml of 40% strength NaOH and extracted three times with 150 ml of ethyl ether. The collected ethyl ether extracts are dried and the solvent is removed in vacuo. 92 g (74% of theory) are obtained as an oil.

(e) 5-Amino-5-desoxy-1.2-O-isopropylidene-6-O-methyl-D-glucofuranose



85 g of the product of example 33 (d) in 500 ml of anhydrous THF are added at −70° C. to 1.5 l of liquid ammonia. 30.5 g of sodium in small pieces are added. After 4 hours the mixture is treated with a total of 106 g of NH_4Cl in 20 portions and kept over night whereby the ammonia evaporates. The residue is treated with methanol, the precipitate filtered off and the solvent removed in vacuo. The residue is treated with ethyl ether/hydrochloric acid, the ether phase extracted three times with a total of 300 ml of diluted hydrochloric acid and the hydrochloric acid phases collected, treated with 200 ml of concentrated NaOH and extracted three times with a total of 600 ml of chloroform. The solution is dried and the solvent removed. The residue is recrystallized from ethyl acetate to yield 47 g (77% of theory) of the product; m.p. 95°–96° C.

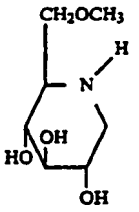
(f) 5-Amino-5-desoxy-6-O-methyl-D-glucose-1-sulfonic acid



10 g of the product of example 33 (e) are dissolved in 50 ml of water. SO_2 is introduced for 2 hours at room temperature and for 15 hours at 60° C. The slurry is treated with methanol, kept for one day, filtered off and

dried. 11.8 g (99% of theory) are obtained; m.p. 154° C. (dec.)

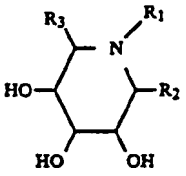
(g) 1-Desoxy-6-O-methylnojirimycin



11 g of the product of example 33 (f) in 90 ml of water are treated with 13.3 g of $Ba(OH)_2.8H_2O$. 3 g of Raney-nickel are added and the mixture is hydrogenated for 10 hours. The mixture is filtered and the solvent is removed in vacuo. The residue is treated with 30 ml of 2N hydrochloric acid, discharged on to a column filled with an acidic ion exchange resin and washed with water. The product is eluted with 0.3N ammonia and obtained after evaporating in vacuo. After recrystallization from ethanol 5.5 g (78% of theory) of m.p. 145° to 146° C. are obtained.

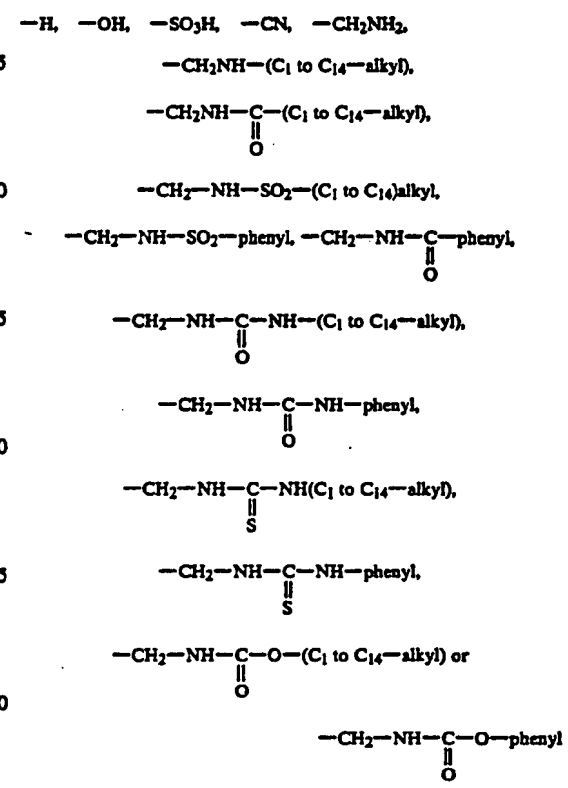
What is claimed is:

1. A compound of the formula



I

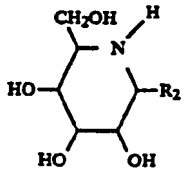
in which R_1 is C_5–C_{30} alkyl, C_2–C_{18} alkenyl, C_2–C_{18} alkinyl, C_3–C_8 cycloalkyl, C_3–C_8 cycloalkenyl, C_3–C_8-cycloalkinyl, phenyl (a), C_1–C_2 and C_7–C_{30} alkyl substituted by phenyl (b) or substituted C_1–C_4-alkyl said C_5–C_{30} alkyl, cycloalkyl, cycloalkenyl and cycloalkinyl being unsubstituted or substituted by hydroxy, C_1–C_4-alkoxy, acyloxy, amino, mono- C_1–C_4 alkylamino, di-C_1–C_4 alkylamino, acylamino, mercapto, C_1–C_4 alkylthio, halogen, C_1–C_4 alkylcarbonyl, carboxyl nitro, cyano, formyl, sulfo, a heterocyclic radical derived from a hexose or pentose, attached to the alkyl moiety directly via a ring atom or via an —O—, —S— or —NH-bridge or naphthyl said phenyl (a) being unsubstituted or substituted by C_1 to C_{10} alkyl, C_1 to C_{10} chloroalkyl, C_1 to C_{10} nitroalkyl, C_1 to C_{10} cyanoalkyl, C_1 to C_{10} alkenyl, hydroxyl, C_1 to C_4 alkoxy, amino, mono-C_1 to C_4 alkylamino, di-C_1–C_4 alkylamino, mercapto, C_1–C_4 alkylthio, carboxyl, C_1–C_4 carbalkoxy, sulfo, C_1–C_4 alkylsulfonyl, phenylsulfonyl, aminosulfonyl, C_1–C_4 alkylaminosulfonyl, di-C_1–C_4 alkylaminosulfonyl, nitro, cyano, formyl, C_1–C_4 alkylcarbonylamino, C_1–C_4 alkylcarbonyl, benzoyl, benzylcarbonyl or phenylethylcarbonyl; said substituted C_1–C_4 alkyl being substituted by hydroxy, C_1–C_4-alkoxy, acyloxy, amino, mono- C_1–C_4 alkylamino, di-C_1–C_4 alkylamino, acylamino, mercapto, C_1–C_4 alkylthio, halogen, C_1–C_4 alkylcarbonyl, carboxyl nitro, cyano, formyl, sulfo, a heterocyclic radical derived from a hexose or pentose, attached to the alkyl moiety directly via a ring atom or via an —O—, —S— or —NH—bridge or naphthyl, said acyl being derived from an aliphatic carboxylic acid having from 1 to 7 C-atoms, a phenyl carboxylic acid, unsubstituted or substituted by carboxy, hydroxy, halogen, C_1 to C_4 alkyl, C_1 to C_4 alkoxy, nitro or amino, or a 5- or 6-membered aromatic heterocyclic carboxylic acid containing from 1 to 3 hetero-atoms each of which is N, O or S, unsubstituted or substituted by C_1 to C_4 alkyl, chlorine, bromine or amino; said naphthyl and phenyl (b) being unsubstituted or substituted by hydroxyl, amino, C_1–C_4 alkylamino, di-C_1–C_4 alkylamino, C_1–C_4alkoxy, nitro, cyano, carboxy, C_1–C_4 alkoxycarbonyl, C_1–C_6 alkyl, halogen, C_1–C_4 alkylthio, mercapto, C_1–C_4 alkylsulfonyl, sulfo, aminosulfonyl or C_1–C_4 alkylaminosulfonyl R_2 is



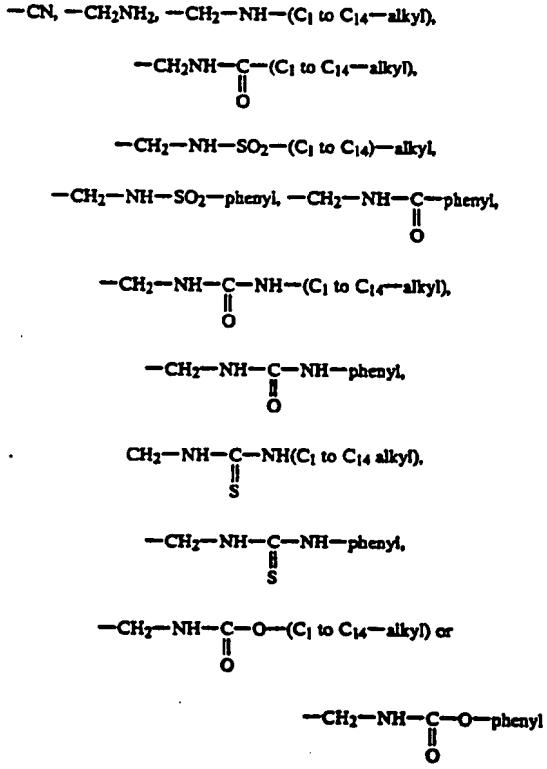
wherein phenyl is unsubstituted or substituted by methyl, ethyl, methoxy, chlorine, bromine or nitro, R_3 is —H, —CH_3, —CH_2OH, —CH_2—NH_2, NHR'—CH_2—, NR'R"—CH_2—, R'CONH—CH_2, R'CO—NR"CH_2—, R'O—CH_2, R'COOCH_2—, R'SO_2NHCH_2—, R'SO_2—NR"CH_2—, R'NH—CO—NH—CH_2—, R'NHCS—NH—CH_2, R'O—CO—NH—CH_2—, wherein R' and R" are the same or different and each has the meaning hydrogen or C_1–C_{30} alkyl, C_2–C_{18} alkenyl, C_2–C_{18} alkinyl, C_3–C_8 cycloalkyl, C_3–C_8 cycloalkenyl, C_3–C_8-cycloalkinyl or phenyl (a), said alkyl, cycloalkyl, cycloalkenyl and cycloalkinyl being unsubstituted or substituted by hydroxy, C_1–C_4-alkoxy, acyloxy, amino, mono- C_1–C_4alkylamino, di-C_1–C_4 alkylamino, acylamino, mercapto, C_1–C_4 alkylthio, halogen, C_1–C_4 alkylcarbonyl, carboxyl, nitro, cyano, formyl, sulfo, a heterocyclic radical derived from a hexose or pentose, attached to the alkyl moiety directly via a ring atom or via an —O—, —S— or —NH—bridge, naphthyl or phenyl (b) said acyl being derived from an aliphatic carboxylic acid having from 1 to 7 C-atoms, a phenyl carboxylic acid, unsubstituted or substituted by carboxy, hydroxy, halogen, C_1 to C_4 alkyl, C_1 to C_4 alkoxy, nitro or amino, or a 5- or

6-membered aromatic heterocyclic carboxylic acid containing from 1 to 3 hetero-atoms each of which is N, O or S, unsubstituted or substituted by C_1 to C_4 alkyl, chlorine, bromine or amino; said phenyl (a) being unsubstituted or substituted by C_1 to C_{10} alkyl, C_1 to C_{10} chloroalkyl, C_1 to C_{10} nitroalkyl, C_1 to C_{10} cyanoalkyl, C_1 to C_{10} alkenyl, hydroxyl, C_1 to C_4 alkoxy, amino, mono-C_1 to C_4 alkylamino, di-C_1-C_4alkylamino, mercapto, C_1-C_4alkylthio, carboxyl, C_1-C_4-carbaloxy, sulfo, C_1-C_4alkylsulfonyl, phenylsulfonyl, aminosulfonyl, C_1-C_4 alkylaminosulfonyl, di-C_1-C_4alkylaminosulfonyl, nitro, cyano, formyl, C_1-C_4 alkylcarbonylamino, C_1-C_4 alkylcarbonyl, benzoyl, benzylcarbonyl or phenylethylcarbonyl; said napthyl and phenyl (b) being unsubstituted or substituted by hydroxyl, amino, C_1-C_4 alkylamino, di-C_1-C_4 alkylamino, C_1-C_4alkoxy, nitro, cyano, carboxy, C_1-C_4 alkoxycarbonyl, C_1-C_6 alkyl, halogen, C_1-C_4 alkylthio, mercapto, C_1-C_4 alkylsulfonyl, sulfo, aminosulfonyl or C_1-C_4 alkylaminosulfonyl.

2. A compound of the formula

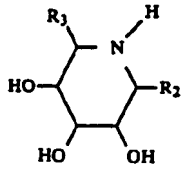


wherein R_2 is

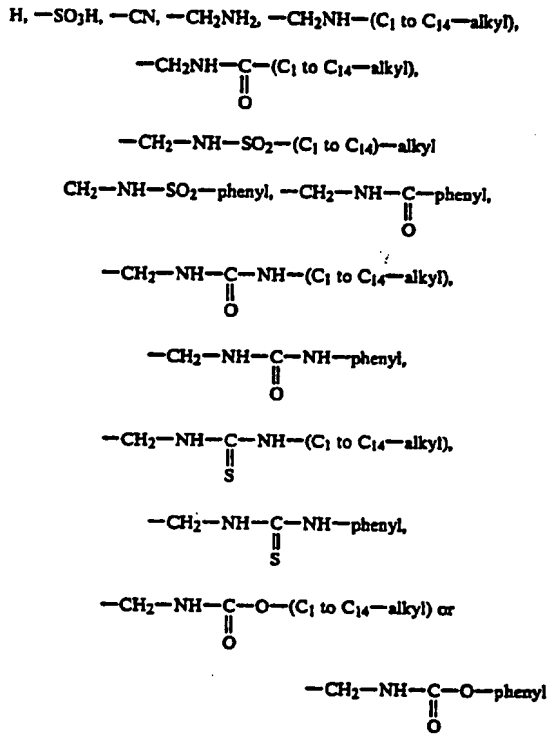


wherein phenyl is unsubstituted or substituted by methyl, ethyl, methoxy, chlorine, bromine, or nitro.

3. A compound of the formula



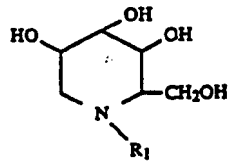
wherein R_2 is



wherein phenyl is unsubstituted or substituted by methyl, ethyl, methoxy, chlorine, bromine or nitro and R_3 is CH_2—NH_2, —CH_2—NHR', —CH_2—NR'R"—, —CH_2—NHCOR', —CH_2—NR"—COR', —CH_2OR', —CH_2—OCOR', —CH_2—NHSO$_2$R', —CH_2—NR"—SO$_2$R', —CH_2—NHCONH$_2$, —CH_2—NHCONHR', —CH_2—NHCSNH$_2$, —CH_2—NHCSNHR', —CH_2—NH—COOR' wherein R' and R" are the same or different and each is C_1-C_{30} alkyl, C_2-C_{18} alkenyl, C_2-C_{18} alkinyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, C_3-C_8-cycloalkinyl or phenyl (a), said alkyl, cycloalkyl, cycloalkenyl and cycloalkinyl being unsubstituted or substituted by hydroxy, C_1-C_4-alkoxy, acyloxy, amino, mono-C_1-C_4alkylamino, di-C_1-C_4 alkylamino, acylamino, mercapto, C_1-C_4 alkylthio, halogen, C_1-C_4 alkylcarbonyl, carboxyl, nitro, cyano, formyl, sulfo, a heterocyclic radical derived from a hexose or pentose, attached to the alkyl moiety directly via a ring atom or via an —O—, —S— or —NH-bridge, naphthyl or phenyl (b) said acyl being derived from an aliphatic carboxylic acid having from 1 to 7 C-atoms, a phenyl carboxylic acid, unsubstituted or substituted by carboxy, hydroxy, halogen, C_1 to C_4 alkyl, C_1 to C_4 alkoxy, nitro or amino, or a 5- or 6-membered aromatic heterocyclic carboxylic acid containing from 1 to 3 heteroatoms each of which is N, O or S, unsubstituted or substituted by C_1 to C_4 alkyl, chlorine, bromine or

amino; said phenyl (a) being unsubstituted or substituted by C_1 to C_{10} alkyl, C_1 to C_{10} chloroalkyl, C_1 to C_{10} nitroalkyl, C_1 to C_{10} cyanoalkyl, C_1 to C_{10} alkenyl, hydroxyl, C_1 to C_4 alkoxy, amino, mono-C_1 to C_4 alkylamino, di-C_1–C_4alkylamino, mercapto, C_1–C_4alkylthio, carboxyl, C_1–C_4-carbalkoxy, sulfo, C_1–C_4alkylsulfonyl, phenylsulfonyl, aminosulfonyl, C_1–C_4 alkylaminosulfonyl, di-C_1–C_4alkylaminosulfonyl, nitro, cyano, formyl, C_1–C_4 alkylcarbonylamino, C_1–C_4 alkylcarbonyl, benzoyl, benzylcarbonyl or phenylethylcarbonyl; said naphthyl and phenyl (b) being unsubstituted or substituted by hydroxyl, amino, C_1–C_4 alkylamino, di-C_1–C_4 alkylamino, C_1–C_4alkoxy, nitro, cyano, carboxy, C_1–C_4 alkoxycarbonyl, C_1–C_6 alkyl, halogen, C_1–C_4 alkylthio, mercapto, C_1–C_4 alkylsulfonyl, sulfo, aminosulfonyl or C_1–C_4 alkylaminosulfonyl.

4. A compound of the formula



wherein R_1 is C_1–C_2 and C_7–C_{30} alkyl substituted by phenyl, said phenyl being unsubstituted or substituted by hydroxyl, amino, C_1–C_4 alkylamino, di-C_1–C_4 alkylamino, C_1–C_4 alkoxy, cyano, carboxy, C_1–C_4 alkoxycarbonyl, C_1–C_6 alkyl or halogen.

5. A compound according to claim 1, in which R_2 is —H, —SO_3H or —CN.

6. A compound according to claim 5 in which R_2 is —H.

7. A compound according to claim 1, in which R_3 is —H, —CH_2OH, —CH_3, —CH_2NH_2, —CH_2—NH or CH_2—O—(C_1–C_6-alkyl).

8. A compound according to claim 1 in which R_3 is —CH_2OH.

9. A compound according to claim 1 in which R_2 is hydrogen and R_3 is —CH_2OH.

10. A compound of claim 1 wherein R_1 is C_1–C_4 alkyl substituted by hydroxy or mercapto.

11. A compound according to claim 1 which is N-methyl-1-norjirimycin, n-ethyl-1-nojirimycin, N-n-butyl-1-nojirimycin, N-benzyl-1-nojirimycin, N-allyl-1-nojirimycin, N-(β-methoxy-ethyl)-1-nojirimycin, N-n-pentyl-1-desoxynojirimycin, N-n-hexyl-1-desoxynojirimycin, N-benzyl-1-desoxynojirimycin, N-allyl-1-desoxy-nojirimycin, N-(β-methoxy-ethyl)-1-desoxynojirimycin, N-methyl-1-desoxynojirimycin-1-sulphonic acid, N-octyl-1-desoxynojirimycin, N-nonyl-1-desoxy-nojirimycin, 1-tosylaminomethyl-1-desoxy nojirimycin, N-methyl-1-tosylaminomethyl-1-desoxynojirimycin, N-nonyl-1-acetylaminomethyl-1-desoxynojirimycin, N-methyl-benzoylaminomethyl-1-desoxynojirimycin, N-propargyl-1-desoxynojirimycin or N-(2-methylmercaptoethyl)-1-desoxy-nojirimycin.

12. A compound of claim 1 which is N-(n-Heptyl)-1-desoxynojirimycin.

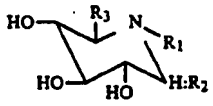
13. A compound of claim 1 which is N-Benzyl-1-desoxynojirimycin.

14. A compound of claim 1 which is N-(β-Hydroxyethyl)-1-desoxynojirimycin.

15. A compound of claim 1 which is N-(5'hydroxy-n-pentyl)-1-desoxynojirimycin.

16. A compound of claim 1 which is N-(β-Hydroxypropyl)-1-(desoxynojirimycin).

17. A compound according to claim 1 which has the steric formula



18. A pharmaceutical composition for the treatment of diabetes, hyperlipaemia or adiposity containing as an active ingredient an effective amount for the treatment of diabetes, hyperlipaemia or adiposity of a compound according to claim 1 in admixture with a solid or liquefied gaseous diluent or in admixture with a liquid diluent other than a solvent of a molecular weight less than 200 except in the presence of a surface-active agent.

19. A pharmaceutical composition for the treatment of diabetes, hyperlipaemia or adiposity containing as an active ingredient an effective amount of a compound according to claim 1 in the form of a sterile or physiologically isotonic aqueous solution.

20. A composition according to claim 18 or 19 containing from 0.5 to 95% by weight of the said active ingredient.

21. A medicament in dosage unit form for the treatment of diabetes, hyperlipaemia or adiposity comprising an effective amount for the treatment of diabetes, hyperlipaemia or adiposity of a compound according to claim 1 and an inert pharmaceutical carrier.

22. A medicament of claim 21 in the form of tablets, pills, dragees, capsules, ampoules, or suppositories.

23. A pharmaceutical composition for the treatment of diabetes, hyperlipaemia or adiposity containing as an active ingredient an effective amount for the treatment of diabetes, hyperlipaemia or adiposity of a compound according to claim 17 in admixture with a solid or liquefied gaseous diluent or in admixture with a liquid diluent other than a solvent of a molecular weight less than 200 except in the presence of a surface-active agent.

24. A pharmaceutical composition for the treatment of diabetes, hyperlipaemia or adiposity containing as an active ingredient an effective amount for the treatment of diabetes, hyperlipaemia or adiposity of a compound according to claim 17 in the form of a sterile or physiologically isotonic aqueous solution.

25. A medicament in dosage unit form comprising an effective amount for the treatment of diabetes, hyperlipaemia or adiposity of a compound according to claim 17 and an inert pharmaceutical carrier.

26. A medicament of claim 25 in the form of tablets, pills, dragees, capsules, ampoules, or suppositories.

27. A method of combating adiposity, diabetes and/or hyperlipaemia in warm-blooded animals which comprises administering to the said animal an effective amount for the treatment of diabetes, hyperlipaemia or adiposity of an active compound according to claim 1 either alone or in admixture with a diluent or in the form of a medicament.

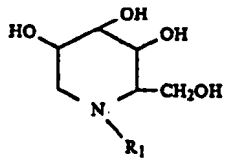
28. A method according to claim 27 in which the active compound is administered in an amount of 0.01 mg to 100 mg per kg body weight per day.

29. A method according to claim 28 in which the animal is a ruminant.

30. A method according to claim 27 in which the active compound is administered orally.

31. A method of combating adiposity, diabetes and/or hyperlipaemia in warm-blooded animals which comprises administering to the animals an effective amount for the treatment of diabetes, hyperlipaemia or adiposity of an active compound according to claim 17 either alone or in admixture with a diluent or in the form of a medicament.

32. A compound of the formula:



wherein R_1 is C_2–C_{18} alkenyl.

* * * * *

Assignment

EXHIBIT C

For valuable consideration, the receipt and adequacy of which is hereby acknowledged,

We, 1) Bodo Junge, 2) Hans Peter Krause, 3) Lutz Müller,
4) Walter Puls,

of 1) Wilkhausstrasse 123, D 56 Wuppertal-2, Germany
2) Wilkhausstrasse 107, D 56 Wuppertal-2, Germany
3) Kronprinzenallee 111, D 56 Wuppertal-1, Germany
4) In den Birken 75, D 56 Wuppertal-1, Germany

hereby sell, assign, and transfer unto BAYER AKTIENGESELLSCHAFT, a corporation of Germany, located at Leverkusen, Germany, the entire right, title, and interest in and to our application for Letters Patent of the United States, executed concurrently herewith, entitled NEW 3,4,5-TRIHYDROX PIPERIDINE COMPOUNDS, THEIR PRODUCTION AND THEIR MEDICINAL USE

and our entire right, title, and interest in and to all our inventions, whether joint or sole, disclosed in said application for Letters Patent, and in and to all divisional or continuation applications that may be filed for United States Letters Patent for any of said inventions, and in and to all patents that may be granted on the foregoing applications, and we hereby agree, whenever requested, to communicate to said assignee, its successors and assigns, any facts known to us respecting said inventions, to testify in any legal proceedings, and to execute all applications or papers necessary to obtain and maintain proper patent protection on said inventions in the United States.

Signed at Wuppertal-1, Germany

this 14th day of August 1978

Witness

Witness

1) Bodo Junge

2) Hans Peter Krause

3) Lutz Müller

4) Walter Puls

RECORDED
PATENT & TRADEMARK OFFICE
AUG 23 1978

Donald W. Banner
COMMISSIONER OF PATENTS

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,639,436 Page 1 of 3

DATED : January 27, 1987

INVENTOR(S) : Bodo Junge, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 7, line 30	Delete "P_3" and substitute --R_3--
Col. 14, line 38	Delete "Ransey" and substitute --Raney--
Col. 17, line 34	Delete "ahgent" and substitute --agent--
Col. 37, line 10	Delete "eedible" and substitute --edible--
Col. 40, line 16	Delete "round" and substitute --found--
Col. 40, line 29	Delete "butylraldehyde" and substitute--butyraldehyde--
Col. 46, line 34	Delete "$(CH_2)_9$" and substitute --$(CH_2)_8$--
Col. 51, line 2, after "Example 8"	Insert --1-Desoxynojirimycin-1-carboxylic acid ethyl ester--
Col. 51, line 29, after "Example 9"	Insert -- N-Methyl-1-desoxynojirimycin-1-carboxylic acid ethylester--
Col. 51, line 45, after "Example 10"	Insert -- 1-Desoxynojirimycin-1-carboxylic acid amide --
Col. 52, line 2, after "Example 11"	Insert -- 1-Desoxynojirimycin-1-carboxylic acid benzylamide --
Col. 52, line 21, after "Example 12"	Insert -- N-Methyl-1-desoxynojirimycin-1-carboxylic benzyl amide --
Col. 52, line 35, after "Example 13"	Insert -- 1-Aminomethyl-1-desoxynojirimycin --
Col. 52, line 53, after "Example 14"	Insert --1-Acetamidomethyl-1-desoxynojirimycin --
Col. 53, line 6, after "Example 15"	Insert -- N-Methyl-1-acetamidomethyl- --

Bayer 3530 JBK

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,639,436

DATED : January 27, 1987

INVENTOR(S) : Bodo Junge, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 53, line 21, after "Example 16"	Insert -- 1-Benzoylaminomethyl-1-desoxynojirimycin --
Col. 53, line 35, after "Example 17"	Insert -- N-Methyl-1-benzoylamino-1-desoxynojirimycin --
Col. 53, line 50, after "Example 18"	Insert -- 1-Tosylaminomethyl-1-desoxynojirimycin --
Col. 54, line 2, after "Example 19"	Insert -- N-Methyl-1-tosylamino-methyl-1-desoxynojirimycin --
Col. 54, line 17, after "Example 20"	Insert -- 1-(N'-Phenylureidomethyl)-1-desoxynojirimycin --
Col. 54, line 38, after "Example 21"	Insert -- N-(1-Desoxynojirimycinyl)-acetic acid-6-lactone --
Col. 54, line 56, after "Example 22"	Insert -- N-(1-Desoxynojirimycinyl)-acetic acid benzylamide --
Col. 55, line 10, after "Example 23"	Insert -- 1-Hydroxymethyl-1-desoxynojirimycin --
Col. 55, line 41, after "Example 24"	Insert -- 6-O-Benzoyl-1-desoxynojirimycin --

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,639,436 Page 3 of 3

DATED : January 27, 1987

INVENTOR(S) : Bodo Junge, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 62, line 7 Delete "methylα" and substitute -- methyl- α --

Signed and Sealed this

Nineteenth Day of May, 1987

Attest:

Priscilla A. Fuller

Attesting Officer

DONALD J. QUIGG

Commissioner of Patents and Trademarks

6/17/83	IND submission (with protocol 83-052)
6/22/83	IND received by FDA
7/22/83	IND effective date
8/31/83	Information amendment:chemistry
9/20/83	Protocol amendment: new protocol 83-081
12/7/83	Protocol amendment: new protocol 83-077
2/21/84	Protocol amendment: new protocol 83-078
4/25/84	Protocol amendment: new protocol 83-113
5/4/84	Protocol amendment: new protocol 83-112
5/16/84	Protocol amendment: new protocol 83-103
6/21/84	Protocol amendment: new protocol 84-013
8/27/84	Information amendment: clinical
8/30/84	Information amendment: clinical
6/25/85	Annual Report
7/29/86	Annual Report
6/15/87	Annual Report
1/20/88	FDA meeting to provide draft protocols
3/15/88	Information amendment: chemistry
4/6/88	Protocol amendment: new protocols 87-056, 87-057
5/17/88	Information amendment - pharmacology/toxicology; clinical
7/22/88	Annual Report

9/27/88	Letter to FDA: response to request for information
1/26/89	Information amendment: pharmacology/toxicology; clinical
4/4/89	Information amendment: pharmacology/toxicology; clinical
6/21/89	Information amendment: pharmacology/toxicology; clinical
7/14/89	Annual Report
8/15/89	Information amendment: pharmacology/toxicology; clinical
2/7/90	Information amendment: pharmacology/toxicology; clinical
8/14/90	Annual Report
8/28/90	Information amendment: pharmacology/toxicology; clinical
9/10/90	Information amendment: clinical
11/12/90	Letter to FDA: response to request for information
12/4/90	Information amendment: pharmacology/toxicology; clinical
1/8/91	Information amendment: clinical
2/12/91	Information amendment: clinical
4/11/91	Letter to FDA: response to request for information
7/24/91	Information amendment: clinical
8/12/91	Information amendment: clinical
8/19/91	Annual Report
10/3/91	FDA meeting: end of Phase II meeting
10/16/91	Information amendment: clinical
1/28/92	Information amendment: pharmacology/toxicology; clinical

4/27/92	Information amendment: clinical
5/11/92	Information amendment: pharmacology/toxicology
5/28/92	Information amendment: pharmacology/toxicology
6/2/92	Letter to FDA: response to request for information
6/10/92	FDA meeting: Pre-Phase III meeting
7/17/92	Annual Report
7/28/92	Protocol amendment: new protocols 92-005, 92-009
8/5/92	Information amendment: chemistry; response to request for information
8/12/92	Protocol amendment: new protocol 92-006
9/2/92	Information amendment: chemistry
11/18/92	Protocol amendment: new protocol 92-014
12/1/92	Information amendment: chemistry
12/14/92	Information amendment: chemistry
12/21/92	Protocol amendment: new protocol 92-024
1/19/93	Information amendment: chemistry
2/12/93	Information amendment: clinical
2/16/93	Protocol amendment: new protocol 92-036
4/19/93	Information amendment: chemistry
5/12/93	Information amendment: clinical
7/6/93	Protocol amendment: new protocols 92-015, 92-016
7/12/93	Annual Report

8/25/93	Protocol amendment: new protocols (93-027, 93-028)
8/30/93	Information amendment: clinical
10/27/93	Protocol amendment: new protocols (x92-006, x92-009)
12/20/93	Information amendment: clinical
7/29/94	Protocol amendment: new protocol: x92-014
8/11/94	Annual Report
10/18/94	Information amendment: clinical
1/9/95	Information amendment: pharmacology/toxicology; clinical
4/19/95	Information amendment: pharmacology/toxicology; clinical
5/4/95	FDA meeting: pre-NDA meeting

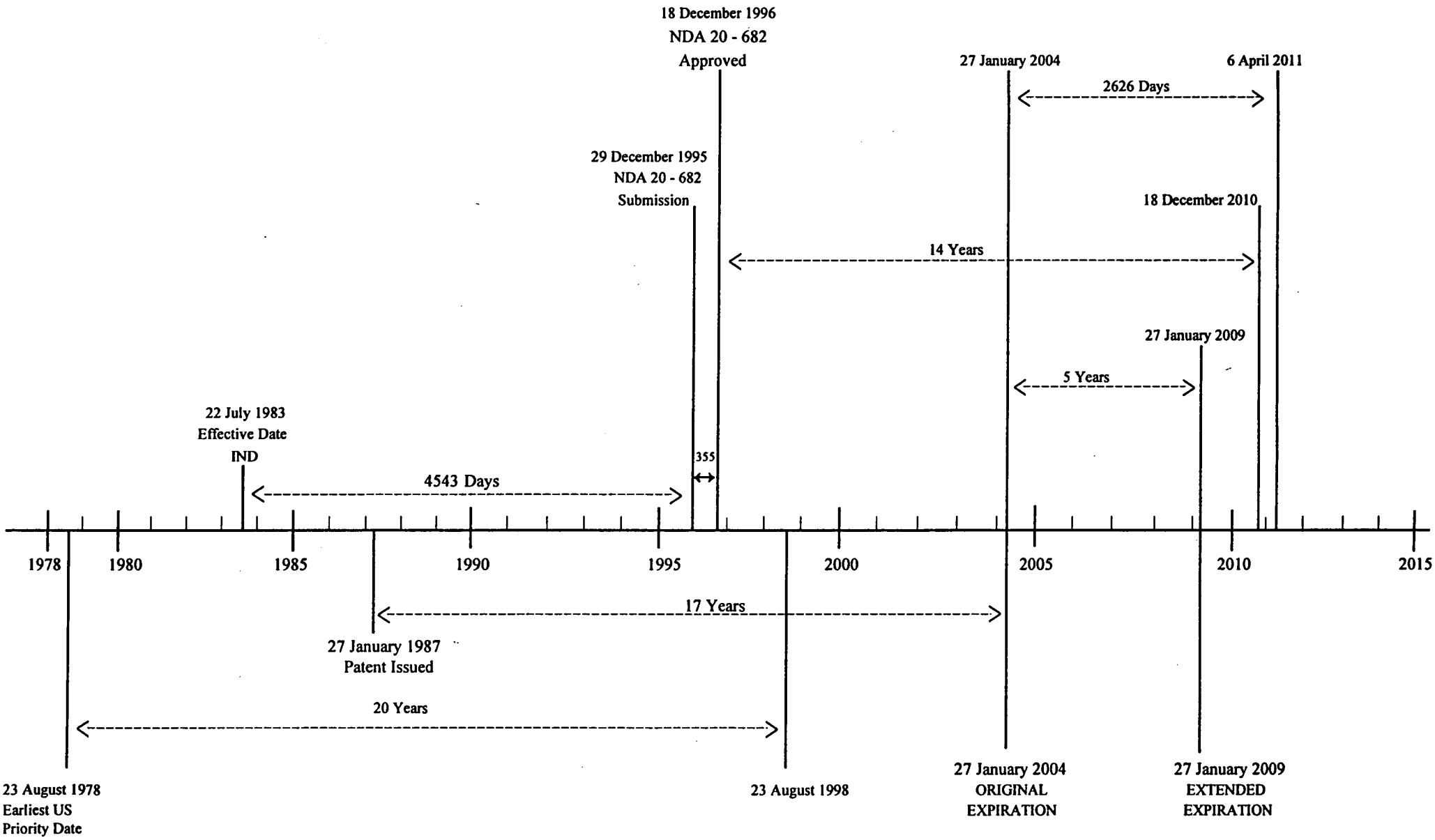
12/8/95	Request from FDA re: statistical analyses
12/28/95	NDA submitted
1/11/96	FDA letter acknowledging receipt of NDA on 12/29/95
1/18/96	Inquiry from FDA re: formulations
1/19/96	Response to FDA inquiry of 1/18/96
1/22/96	Inquiry from FDA re: Chemistry/Manufacturing/Controls
1/22/96	Response to inquiry of 1/22/96
1/22/96	Request from FDA: Send additional copy of NDA summary
1/22/96	Response to request of 1/22/96 sent to FDA
1/22/96	Request from different FDA reviewer for duplicate NDA Summary
1/22/96	Duplicate NDA Summary sent to second FDA reviewer
2/2/96	Request for clinical site information
2/7/96	Response to 2/2/96 FDA request
2/7/96	Response to 12/8/95 FDA request
2/12/96	Request from FDA re: specific Case Report Forms and Adverse Experiences
2/16/96	Response to request of 2/12/96 sent to FDA
2/27/96	Inquiry from FDA re: pharmacodynamic study, requesting pharmacokinetic information on diskette, and Environmental Assessment
3/21/96	Request for clarification re: clinical issue
3/25/96	Response to 3/21/96 FDA inquiry
3/25/96	Telephone discussion of bioequivalence issue
3/26/96	Request from FDA re: carcinogenicity data on diskette.

4/1/96	Telephone discussion of bioequivalence issue
4/3/96	Diskette with pharmacokinetic information sent to FDA in response to request of 2/27/96
4/8/96	Meeting with FDA re: bioequivalence
4/9/96	Inquiry from FDA re: power calculations
4/11/96	Inquiry from FDA re: clinical question: ECGs
4/26/96	4 month safety update submitted
5/1/96	Sent power calculations for possible bioequivalence or pharmacodynamic study in response to request of 4/9/96
5/6/96	Inquiry from FDA requesting carcinogenicity data in specific format on diskette
5/7/96	Request from FDA re: overheads from 4/8/96 meeting
5/8/96	ECGs submitted in response to FDA inquiry of 4/11/96
5/9/96	Overheads submitted to FDA in response to 5/7/96 request
5/10/96	Response to FDA inquiry at 4/8/96 meeting
5/13/96	Diskettes with additional pharmacokinetic information sent to FDA in response to 2/27/96 request
5/13/96	Amended Environmental Assessment sent to FDA
5/24/96	Inquiry from FDA requesting bioequivalence data
6/4/96	Carcinogenicity data submitted to FDA in response to 5/6/96 request
6/18/96	Response to FDA inquiry of 5/24/96
6/27/96	Request from FDA for Chemistry/Manufacturing/Controls data
7/2/96	Response to FDA inquiry of 6/27/96
7/29/96	Request from FDA for new diskette containing statistical information

8/1/96	Inquiry from FDA re: NDA summary
8/1/96	Response to FDA inquiry of 8/1/96
8/2/96	Response to FDA request of 7/29/96
8/9/96	Request from FDA re: statistical analyses
8/12/96	Response to FDA inquiry of 8/9/96
8/16/96	Response (additional information) to FDA inquiry of 8/9/96
8/26/96	Request from FDA for two copies of diskette containing miglitol Package Insert
8/28/96	Inquiry from FDA re: chemistry
8/30/96	Response sent to FDA inquiry of 8/28/96
8/30/96	Two copies of diskette containing miglitol Package Insert to FDA sent in response to 8/26/96 request
9/20/96	Inquiry from FDA re: Chemistry/Manufacturing/Controls, biopharmaceutics, Environmental Assessment
9/30/96	Inquiry from FDA re: Package Insert
10/3/96	Two telephone calls to FDA in response to 9/20/96 FDA inquiry
10/10/96	Telephone conference with FDA (follow up to 9/30 inquiry)
10/11/96	Response to 9/30/96 Chemistry/Manufacturing/Controls comments from FDA
10/17/96	Telephone conference with FDA re: dissolution
10/22/96	Request from FDA: Submit revised Package Insert as NDA amendment
10/23/96	Revised Package Insert submitted in response to 10/22/96 request
10/24/96	Response to FDA inquiry of 10/17/96
10/28/96	Inquiry from FDA re: Environmental Assessment

10/29/96	Response to 10/28/96 FDA request
11/6/96	Telephone conference with FDA re: dissolution specifications
11/7/96	Inquiry from FDA re clinical issues
11/7/96	Response to 11/7/96 FDA inquiry
11/12/96	Minutes of 11/6/96 telephone conference submitted to FDA
11/13/96	Request from FDA re: Package Insert
11/26/96	Response to request of 11/13/96 submitted to FDA
12/9/96	Telephone conference with FDA: Package Insert
12/10/96	Telephone conference with FDA: Package Insert
12/11/96	Revised Package Insert submitted.
12/12/96	FDA request re: carcinogenicity data
12/13/96	Response to FDA inquiry of 12/12/96
12/13/96	Request from FDA for weight data in toxicology studies
12/13/96	Response to FDA inquiry of 12/13/96
12/13/96	Discussions and/or correspondence with FDA re: proposed revisions to Package Insert
12/16/96	Discussions and/or correspondence with FDA re: proposed revisions to Package Insert
12/17/96	Revised Package Insert submitted
12/18/96	Discussions with FDA re: proposed revisions; final amendment to Package Insert
12/18/96	Revised Package Insert submitted
12/18/96	NDA approved

EXHIBIT F
(Time Line)



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No.: 4,639,436 Issued: 27 January 1987

Patentee: Junge et al. Title: Antidiabetic 3,4,5-Trihydroxypiperidines

Assignee: Bayer Aktiengesellschaft

Date: 12 February 1997

Box Patent Extension
Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

SUPPLEMENT TO APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC 156 et seq. AND 37 CFR 1.710 et seq.

Transmitted herewith as requested by the Examiner is a corrected Declaration amended to included the language required by 37 CFR 1.740(b)(2) which was inadvertently omitted in the original declaration.

The original Declaration will be hand-carried to the PTO on 13 February 1997, together with a certified copy.

The Commissioner is hereby authorized to charge any fees required as a result of this submission to Deposit Account No. 13-3372. A duplicate of this sheet will be enclosed with the original.

Respectfully submitted,

Barbara A. Shimei

Barbara A. Shimei, Esq.
Registration No. 29,862
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516

Phone: (203) 812-2786
Fax: (203) 812-5492

(17) **DECLARATION OF ATTORNEY:**

I hereby declare that all statements made herein of my own knowledge are true; that all statements made on information and belief are believed to be true; that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application; that I am a patent attorney authorized to practice before the United States Patent and Trademark Office; that Bayer Corporation has been granted certain rights under the subject patent by its parent company Bayer AG; that Bayer Corporation's predecessor in interest Miles Inc. was the sponsor of the subject IND and Bayer Corporation was the sponsor of the subject NDA; that Miles Inc. and Bayer Corporation was/is an affiliate of Bayer AG and sublicensed by Bayer AG to market approved products in the United States; that by virtue of the enclosed Power of Attorney duly signed by Bayer AG I am an authorized designee of Bayer AG for the purpose of submitting this application for patent term extension, and hence, have the authority to submit and prosecute this application on behalf of Bayer AG; that I have reviewed and understand the contents of the application that is being submitted herewith; that I believe the subject patent is subject to extension pursuant to 37 CFR 1.710; that I believe an extension of the length claimed is justified under 35 USC 156 and the applicable regulations; and that I believe that the subject patent meets the conditions for term extension as set forth in 37 CFR 1.720.

Respectfully submitted,

Barbara A. Shimei

Barbara A. Shimei, Esq.
Reg. No. 29,862
Bayer Corporation
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West Haven, CT 06516

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Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

FAX TRANSMISSION COVER SHEET
PATENT/LEGAL DEPARTMENT
FAX NUMBER: (203) 812-5492
TELEPHONE NUMBER: (203) 812-2786

TO: Karen Tyson/Patent & Trademark Office **DATE** February 12, 1997

FAX #: (703)308-6916 **PHONE NO.:** (703)306-3159

FROM: Barbara A. Shimei **NO. OF PAGES(including cover)** 3

SUBJECT: U.S. Patent No. 4,639,436 Patent Term Extension

If there are any problems with this transmission, please contact Karen Fiedler at (203) 812-2305.

ORIGINAL

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No.: 4,639,436 Issued: 27 January 1987

Patentee: Junge et al. Title: Antidiabetic 3,4,5-Trihydroxypiperidines

Assignee: Bayer Aktiengesellschaft

Date: 12 February 1997

Box Patent Extension
Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

SUPPLEMENT TO APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC 156 et seq. AND 37 CFR 1.710 et seq.

Transmitted herewith as requested by the Examiner is a corrected Declaration amended to included the language required by 37 CFR 1.740(b)(2) which was inadvertently omitted in the original declaration.

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(17) **DECLARATION OF ATTORNEY:**

I hereby declare that all statements made herein of my own knowledge are true; that all statements made on information and belief are believed to be true; that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application; that I am a patent attorney authorized to practice before the United States Patent and Trademark Office; that Bayer Corporation has been granted certain rights under the subject patent by its parent company Bayer AG; that Bayer Corporation's predecessor in interest Miles Inc. was the sponsor of the subject IND and Bayer Corporation was the sponsor of the subject NDA; that Miles Inc. and Bayer Corporation was/is an affiliate of Bayer AG and sublicensed by Bayer AG to market approved products in the United States; that by virtue of the enclosed Power of Attorney duly signed by Bayer AG I am an authorized designee of Bayer AG for the purpose of submitting this application for patent term extension, and hence, have the authority to submit and prosecute this application on behalf of Bayer AG; that I have reviewed and understand the contents of the application that is being submitted herewith; that I believe the subject patent is subject to extension pursuant to 37 CFR 1.710; that I believe an extension of the length claimed is justified under 35 USC 156 and the applicable regulations; and that I believe that the subject patent meets the conditions for term extension as set forth in 37 CFR 1.720.

Respectfully submitted,

Barbara A. Shimei

Barbara A. Shimei, Esq.
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